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# Orphan Drugs and Corporate Social Responsibility: Which Possible Future Scenarios?

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## 1. Introduction

Orphan drugs (OD) are developed to cure rare diseases or disorders. Definition of "rare disease" may vary from country to country. A disease is defined rare if affects 200,000 people or less in United States (US) or 10,000 persons or less in the European Union (EU) (Orphanet, 2012). An estimated 5 to 10% of the global population is affected by rare diseases, of which about 55 million live in the US and EU (Clinuvel, 2014). As of 2015, almost 7,000 rare diseases have been listed, whereas available OD are only for approximately 400 of them (Phrma, 2013). About 50% of the patients are children, of which a large part suffers from genetic or cancer-related pathologies. These illnesses frequently appear in an early stage of childhood and are often deadly or debilitating. Globally, pharmaceutical companies were reluctant to invest in the development of OD since the small consumers' market might not even allow the company to recoup the initial investment. Indeed, compared to the commercial potential of common diseases, the continued financial support needed for ODs development is high. Moreover, since there is a limited population available to study, it is more difficult to find evidence for the safety and effectiveness of these drugs (Onakpoya I.J., 2015).

However, incentives and support of governments, policy makers and regulatory agencies, mainly in the US and EU, made the OD market more attractive to pharma companies who invest in the sector. Nevertheless, as the approvals for ODs are usually based on small sample sized studies, of shorter duration and potentially using surrogate endpoints, a high incidence of post-marketing safety issues and expanded observational and epidemiological studies after approval are deemed necessary, thereby increasing financial burden and commercial uncertainty. These post-marketing commitments are thus crucial to address the ODs clinical efficacy (FDA, 2015).

## 2. What is an Orphan Drug?

According to Orpha.net, one of the most authoritative portal for rare diseases and ODs, "the so-called 'orphan drugs' are intended to treat diseases so rare that sponsors are reluctant to develop them under usual marketing conditions as in general developing a drug to treat a rare disease does not allow the recovery of the capital invested for its research." (Orphanet, 2015).

Therefore, ODs should be defined as developed by the pharma industry mainly to respond to a public health need and not for economic reasons.

In defining ODs three cases may arise:

- **Cure for rare diseases and disorders**
  These products are developed and aimed to treat patients affected by rare diseases or disorders for which there is no alternative satisfactory treatment available yet (Orphanet, 2015).

- **Drugs discontinued for reason linked to financially viability, therapeutic ineffectiveness and unexpected side effects**
  E.g. Thalidomide, a widely used hypnotic drug, was withdrawn from the market some years ago when its high teratogenic risk for fetuses was discovered. However, for certain diseases as leprosy or lupus erythematosus no alternative satisfactory treatments with similar analgesic properties are available (Orphanet, 2015).

- **Undeveloped drugs**
  Products often remain undeveloped either because their R&D process is not patentable or because the markets to which are supposedly addressed are not economically convenient (e.g. Third-World Countries) (Orphanet, 2015).

## 3. Orphan Drug incentives for research and development (R&D)

With the intent of stimulating and encourage R&D in the ODs' sector, worldwide drug regulatory authorities, agencies and governments have implemented incentives for pharmaceutical, health and biotechnology industries. The first were the United States that signed the Orphan Drug Act in 1983, followed, in order, by Japan in 1993, Australia in 1997 and lastly Europe in 1999 when a common policy regarding ODs for all the European Union member countries was adopted (Orphanet, 2015). For the purposes of this research, strategies regarding availably and regulation of ODs in different countries are reported.

### 3.1. Orphan drugs in the United States of America

In the US, the FDA (Food and Drug Administration) created the OOPD (Office of Orphan Products Development) in 1982 to encourage the development of ODs for the treatment of rare disease and disorders.

The US Public Health authorities, signing the 'Orphan Drug Act' (ODA) in 1983, defined a drug as orphan "if used in diseases or circumstances which occur so infrequently in the USA, that there is no reasonable expectation that the cost of developing and making available in the USA a drug for such disease or condition will be recovered from sales in the USA for such drugs." (Orphan Drug Act, 1983).

The ODA is a result of patient organizations' activism leaded by Abbey Meyers. Mayers became a patient advocate in early '80 in response to her daughter's illness Tourette syndrome that had no treatment at the time (Raber, 2006). Since 1983, several amendments were approved, aiming at defining the criteria that an OD must meet in US. The 1984 amendment defined the "low incidence" concept, stating that a rare disease or circumstance in US must affects less than 200,000 individuals or more than 200,000 individuals without it being possible to cover the cost of development and distribution by sales on national territory. In the same amendment, limit of prevalence for a rare condition was set at 7,5/10,000. The 1985 and 1990 amendments extended the orphan products definition to products other than drugs and in particular: biologics, medical devices and medical foods. The 1988 amendment stated that the Marketing Authorization of a product should be submitted by pharma companies before the

application for OD status and that the product must not have been previously approved for the disease or the condition for which the applicant requests the OD status. The 1992 amendment reported that if the drug is theoretically similar to an OD authorized for the same rare disease, the applicant must demonstrate its clinical superiority with regard to prevention, diagnosis or treatment (Orphanet, 2015). Moreover, more than one sponsor can receive designation for the same drug for the same use. However, the seven years marketing exclusivity is given to the first firm that complete the application file. Finally, competitors are not prevented from making the drug available for different uses during the seven year period of exclusivity (Orphanet, 2015).

The 'orphan' status allows the drug sponsor to benefit from incentives for the development of these products that are in detail:

- **Fast track:** allows the review of a new drug application (NDA) or biologics license application (BLA) on a rolling basis with data submitted in modules. Fast track status involves more frequent collaboration with the FDA and accelerates the review process (FDA, 2014).
- **Breakthrough therapy:** a breakthrough therapy is a drug considered alone or in combination with other drugs to treat a severe or life-threatening condition. Breakthrough therapy is so defined when preliminary clinical results indicate that it may offer significant improvements over existing therapies on one or more relevant endpoints, and such a substantial clinical effects are observed early in development. If a drug is designated as a breakthrough therapy, the FDA will speed up its development and review (FDA, 2014).
- **Accelerated approval:** involves the use of surrogate endpoints in pivotal clinical studies. These endpoints may not be well established but must fulfill the criteria to be "reasonably likely to predict clinical benefit." (FDA, 2014).
- **Priority review:** reduces the period of time taken by the FDA to review an NDA or BLA from ten months to six months (FDA, 2014).

These measures generally make the duration from Phase I to launch on the market shorter (3.9 years compared with 5.42 years for non-orphan drugs). Moreover, ODs

would have a higher probability of regulatory success compared with that of non-orphan drugs (93% vs 88%) (Meekings K. N., 2012).

In the US, granting OD status is based upon an application dossier submitted to the Office of Orphan Products Development (OOPD). The FDA has to provide an answer to the applicant within a maximum of 60 days after receiving the application. When the drug is designated as 'orphan', this information is published in the Federal Register. Then the marketing authorization application has to be done before an OD can be marketed (Orphanet, 2015).

In USA, the availability of ODs to patients before being granted a marketing approval is possible in some cases of compassionate use. Indeed, a Treatment Investigational New Drug (t-IND) designation for a limited period of time may be obtained under specific conditions (Orphanet, 2015).

### 3.2. Orphan drugs in Japan

On 1 October 1993, the Japanese Government introduced special provisions relative to research on ODs in the pharmaceutical law. According to these, OD status can be granted to a drug when it fulfills the following two criteria:

- The disease to treat which the drug is developed must be incurable and no possible alternatives must be available; or the efficacy and safety of the drug must be “excellent” in comparison with available drugs (Orphanet, 2015).

- The number of patients affected by this disease in Japan must be less than 50,000 on the Japanese territory. The limit of prevalence for a rare condition in Japan is therefore set at 4/10,000 (Orphanet, 2015).

Multinational and Japanese companies market ODs in Japan, however small and medium size companies account for the most important part of suppliers. On the contrary, public institutes and universities are less involved. The OD status in Japan is granted by the Ministry of Health, Labour and Welfare (MHLW). Scientific

examination pertains to a subcommittee of the Medicinal Products Committee (Orphanet, 2015).

Incentives to ODs providers are in term of R&D, intellectual property and marketing. The Japanese government supports pharma companies at two levels: administrative and financial.

At the administrative level, ODs benefit from a fast-track marketing authorization procedure. In addition, a consultation on development protocols and assistance concerning the preparation of approval applications are provided. Moreover, the registration validity period, which is 4 - 6 years for traditional drugs, is extended to 10 years (Orphanet, 2015).

At the financial level, government funds, such as the Drug Fund for Side-Effects Relief and Research Promotion, are available. These funds give financial assistance to cover up to 50% of the expenditure devoted to R&D. Funding also covers scientific activities, including clinical trials. In addition, a 6% tax reduction for expenses is granted. Companies making profits on sales of ODs must return a proportion of the subsidy granted as a contribution to these funds (Orphanet, 2015).

### 3.3. Orphan drugs in Australia

The Australian Therapeutic Goods Administration (TGA) introduced specific regulations for OD development in 1997, based on those previously adopted by the US FDA. Two requirements must be met for orphan designation:

- The prevalence of the disease should be 2,000 affected individuals or less, or, if the drug is a vaccine or in vivo diagnostic agent, the persons to whom the drug will be administered in Australia are fewer than 2,000 per year at the time the request is made (Orphanet, 2015).

- If the prevalence of a disease is greater than 2,000 individuals, but the sponsor can demonstrate that the marketing of the drug would not be financially viable.

Limit of prevalence for a rare disease in Australia is set at 1.2/10,000 (Orphanet, 2015).

The TGA works in close collaboration with the FDA. Collaboration between the TGA and the EMA (European Medicines Agency) was reinforced in April 2014, when the agencies agreed to share the full assessment reports related to marketing authorizations of orphan medicines. The main characteristics of the OD policy in Australia are (Orphanet, 2015):

- A legal framework for designation

- Waiver of application and evaluation and no annual registration fees

- A five-year exclusivity (under consideration by the Australian jurisdiction).

Regarding the funding of ODs, TGA covers all the costs of the OD designation process, and then balances its expenditures with other components of the health care system overall budget. The health-care financing system in Australia may be an issue in the delivery of ODs to patients. In fact, the cost of ODs may prevent some patients using them. However, Australia has a Pharmaceutical Benefits Scheme, which provides subsidies to make some drugs are more affordable. The place of ODs in such a scheme is actually under discussion among the Australian Health Care Authorities. In Australia, R&D is supported by neither grants nor tax incentives (Orphanet, 2015).

There is no specific law concerning intellectual property for ODs. The legal status is applied to ODs as for any other drug registered for supply in Australia. On the other hand, the TGA covers registration fees (Orphanet, 2015).

### 3.4. Orphan drugs in Europe

Industry and health authorities (EMEA - European Medicines Evaluation Agency) in Europe made efforts to implement incentives to favor the development of ODs. This policy however was adopted much later in Europe than in the US. This was mainly due to the fact that European territory was formerly split-up and its competencies as regard to health were disjointed (Orphanet, 2015). However, the new system of European

Union (EU) marketing authorization, approved in January 1995 and valid for the whole area, made Europe a joint territory. Actual population is about 503 million people, greater than that of the US (318.9 million) (World Bank, 2015).

On December 1999, the European Parliament and Council adopted regulation (CE) N° 141/2000 on ODs according to which an orphan product is defined as "one that is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10,000 persons in the community when the application is made" (EC reg N° 141/2000). The requirement for the disease or condition to be 'life-threatening or chronically debilitating' introduces a difference between EU and US regulations beyond disease prevalence.

As in US, an alternative to designation is to prove that without incentives it is unlikely that the marketing of the product would generate sufficient return to justify the necessary investment. Where alternative treatments exist, the new product must offer significant additional benefit for patients. According to European regulation n° 141/2000, only drugs for human use can be designated as 'orphan drugs' (EC reg N° 141/2000). Drugs designated as orphan are entered in the Community register for Orphan Medicinal Products. In Europe the following regulatory agencies are involved in ODs:

- The Committee for Orphan Medicinal Products (COMP) of the EMA, set up in 2000 to review applications for orphan product designation, to assist the European Commission in drawing guidelines, to assist the Commission in liaising with patient support groups and finally to advise the Commission on policy for orphan medicinal products in the EU. The evaluation process for orphan designation applications by COMP takes a maximum of 90 days from validation (Orphanet, 2015).

- Following orphan designation, the COMP works with the Committee for Medicinal Products for Human Use (CHMP) during the review and approval stages of the process (Orphanet, 2015).

- In 2009, the EMA introduced the Committee for Advanced Therapies (CAT) in accordance with Regulation (EC) No. 1394/2007 to evaluate gene therapy, somatic cell therapy and tissue-engineered products (Orphanet, 2015).

- In 2014, the EU expert group on rare diseases replaced the EU Committee of Experts on Rare Diseases (EUCERD). The expert group was set up to be a Commission Decision (2013/C 219/04) to support EU policy on rare diseases (Orphanet, 2015).

Incentives provided by the EU regulation are:

- **Market exclusivity:** When an orphan product receives a marketing authorization from the EMA, competitive similar products cannot be placed on the market for 10 years. In the case of pediatric drugs the marketing exclusivity is extended to 12 years (Eurodis, 2014).

- **Protocol assistance:** The EMA provides protocol assistance in the form of scientific advice about tests and clinical trials necessary for drug development to pharmaceutical companies. This information is delivered at no cost or at a reduced fee (Eurodis, 2014).

- **Fee reductions:** During the approval process fee waivers for orphan designation and reduced fees are provided. These apply to marketing authorization, inspections, variations and protocol assistance (Eurodis, 2014).

- **EU-funded research:** Pharmaceutical companies developing ODs may be eligible for specific grants from EU and Member State programs as well as initiatives supporting R&D development (Eurodis, 2014).

- **Orphan medicines centralized procedure at European level** (Eurodis, 2014).

However, granting marketing approval in EU does not mean that the drug is automatically available throughout all the European countries. Indeed, the heterogeneous approaches among countries, despite joint efforts, make patients access to ODs in Europe quite complex. Within every country the drug must undergo through numerous steps that condition its management and price. Due to the lack of a comprehensive approach to rare diseases, the European Project for Rare Diseases National Plans Development (EUROPLAN) 2012-2015 has been developed to provide

technical support for implementing national plans/strategies on rare diseases. Moreover, as result of discussions between regulatory agencies in different countries, industry and patient advocacy groups to harmonize various aspects, a joint FDA/EMA application form for orphan product designation is now available (Orphanet, 2015).

As in the US, also in Europe early access to a drug for patients may be possible before its marketing authorization is granted whether appropriate conditions exist (Orphanet, 2015).

Comparisons among incentives adopted in different Countries are reported in the following table.

**Tab. 1 - Incentives for OD Development in Selected Markets**

| | US | EU | Japan | Australia |
|---|---|---|---|---|
| Market exclusivity | 7 years | 10 years | 10 years | 5 years |
| Funding | Yes | Not at EU level | Yes | No |
| Tax credits for clinical research | Yes (50% for clinical costs) | Not at EU level (managed by member states) | Yes (6% of clinical and non-clinical costs) | No |
| Assistance with trial design | Yes | Yes (partial) | Yes | Yes |
| Application fee waivers | Yes | Reduced fees | No | Yes |

*(Source: data from Field M.J., 2011)*

## 4. Porter's Five Forces analysis

Porter's Five Forces analysis permits to better understand the competitive environment and its dynamics and clarifies the strength of a current or potential firm's position in the market or industry (Fontana F., 2013). Forces are intertwined one with the other and change and evolve over the time. Incumbent and potential entrants exercise pressure to Porter's forces through their competitive strategies and interactions (Fontana F., 2013).

Competitive power depends on these five forces:

**1. Threat of New Entrants**: The threat of new entry mainly depends on entry barriers. Entry barriers can be time consuming and cost effecting, making the potential entrants reluctant to enter the market. Barriers to enter the market can be categorized into institutional barriers (created by the law and regulatory agencies e.g. patents and exclusive rights), structural barriers such as economies of scale, of experience and cost advantages held by incumbents and strategic barriers (Fontana F., 2013). Incumbent behavior and practices might results in strategic barriers explicitly aiming to deter new entrants (Fontana F., 2013). Vertical integration often increase economies of scale for incumbent thank to the reduction of the price markup for each of the integrated phases (D'Aveni R. A., 1994).
Also pricing strategies, such as predatory pricing, can be used by incumbents to lower the risk of reducing the strength of their position (Fontana F., 2013).

**2. Threat of Substitution**: Availability and number of substitute products affects the threat of substitution of products or services. Two products are defined as substitute if their cross elasticity of demand is high and positive (Fontana F., 2013). The propensity of customers to substitute products also depends on customer loyalty and switching costs they eventually face.

**3. Bargaining Power of Suppliers**: In order to better understand the industry's competitive environment is fundamental to take into consideration the bargaining power of suppliers and buyers, also defined as vertical competition (Fontana F., 2013). The first depends on the number of supplier available on the market, the level of their

competition and the switching costs for the company. The less the suppliers are concentrated the lower is their bargaining power as their competition increase. On the other hand, the fewer the supplier are, the more incumbent supplied companies rely on them, increasing their bargaining power.

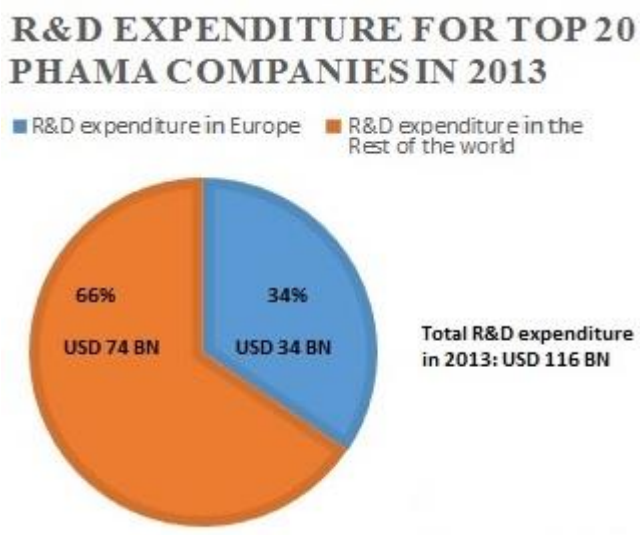
**4. Bargaining Power of Buyers**: It is important to assess how easily buyer can reduce the price of the good that is being sold or the service that is being provided before renouncing to the transaction or more in general terms to determine buyers' ability to exert influence over the company (Collins, 2013).
Similarly to the bargaining power of suppliers, it is strongly dependent on the number of buyers, their concentration and their individual importance to the company. Also, buyers' switching costs influence their bargaining power, decreasing the possibilities of customer shifting from a company's products and services to another's. Other important factors include coordination among buyers and market transparency (Fontana F., 2013).

**5. Intensity of Competitive Rivalry**: It is a necessary element to assess the competitiveness of the sector or industry. Critical factors are the number of competitors and their sizes that determine absolute (only the number) and relative concentration indexes. Other important factors include industry grow rate (if it is low then the rivalry in the industry is higher), industry cost structure (the higher the fixed cost the higher the intensity), and product differentiation (Fontana F., 2013).
In order to reduce the intensity of competition is important for companies to get and sustain a competitive advantage: an advantage over competitors that allow the company who has it to have higher sales and/or margin (Porter M.E., 1998).

### 4.1. Porter's Five Forces analysis of European pharmaceutical industry

#### 1. Threat of New Entrants (Low)

Very high entry barriers characterize the industry. Main barriers are linked to economies of scales; new entrants would face significant entrance costs mainly due to R&D expensive activities. In particular the cost of researching a developing a new chemical




*(Source: Data elaboration from Noor W., 2013)*

or biological entity has been estimated over 1 USD billion in 2012 (Efpia, 2012). Overall, R&D's total expenditure for top 20 pharma firms in 2013 exceeded USD 116 billions, of which more than 34% comes from European firms (USD 40.106 billion) (Noor W., 2013).

Many companies expand through acquisition. For instance, German pharma company Bayer, that never hided its intention to become the world's leader in OTC market, acquired Merck & Co's OTC unit for USD 14.2 billion in October 2014 (Bieri C., 2015). This M&A trend is often linked to the strategic goal of "spreading their R&D expenditure across a greater volume of sales" (Economist, 2008). In addition, drug patents and intellectual property, an example of institutional barrier, are strongly defended by pharma companies. However, many patents of large firms' best-selling drugs are now expiring, making the market more accessible to new entrants that are able to inexpensively produce generic drugs without facing excessive R&D costs (Blanc L., 2014). As an example a USD 10 billion loss in annual sales was expected by Pfizer as "Lipsor" drug patent expired (Duff W., 2011).

**2. Threat of substitution (High)**

Demand for generic versus brand name drugs has increased: the general tightening of health care expenditure in several European countries, often linked to the financial crisis of 2008, together with the expiration of many drug patents determined a strong increase of generic market grow rate and a reduction in the originators market one's. Sustained cost in R&D to

| | Percentage of turnover spent on | | |
|---|---|---|---|
| | R&D | Manufacturing | Marketing |
| Originator companies | 18% | 21% | 21% |
| Generic companies | 7% | 13% | 51% |

*(Source: Blanc L., 2014)*

develop generic drugs, in fact, is not excessive allowing generic producers (usually SMEs) to sell them at a significantly lower price (Blanc L., 2014). Branded drugs are preferred by medical professionals only if generic drugs do not perform as well (Kubachyna O., 2011).

**3. Bargaining power of suppliers (Low)**

The key supplier of the pharma industry is the chemical industry. However, even if the chemical sector is very concentrated it is hard for them to compete in the market as the largest part of their sales are highly standardized products (known as commodities). The result are very inelastic prices for raw chemical materials and low bargaining power (Kubachyna O., 2011).

Large players as the British GlaxoSmithKline often pose a backward integration's threat to supplier in case of inconvenient conditions (Olow J., 2014).

**4. Bargaining power of buyers (High)**

Hospitals and other health care organizations purchase in mass amounts and apply pressure on pharmaceutical organizations to hold prices under control: payers in pharma industry include hospitals, pharmacies, patients and governments (Kubachyna O., 2011).

Especially in Europe, where national health coverage is often provided, as previously reported in the threat of substitution paragraph, governments efforts to promote generics in order to cut and reduce public healthcare budget and low switching costs push pharma companies to lower their drug prices and provide more data about drug's use outcomes (Blanc L., 2014).

**5. Intensity of competitive rivalry (High)**

Concentration ratio in the pharma industry is high. It is characterized by few large players which hold the majority of the market share. In particular, as of 2014, top 20 pharmaceutical firms share 64.4% of the total pharmaceutical market 8 of whom are European and hold a 30.4% global market share (EvaluatePharma, 2015).

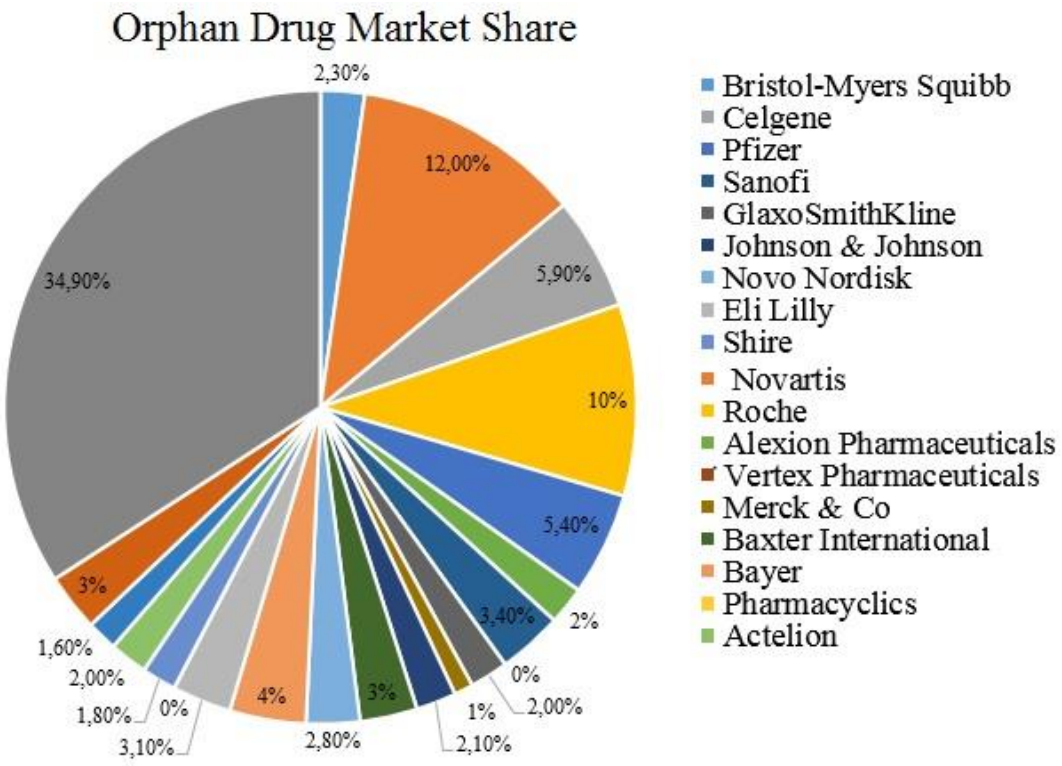

*(Source: Data elaboration from EvaluatePharma, 2015)*

The industry presents high competition among leader companies in the business. The "marketing war" between prescribed drugs for erectile dysfunction (Pfizer's Viagra, Bayer & GlaxoSmithKline's Levitra and Eli Lilly & ICOS's Cialis), provides an example of low level of differentiation for certain drugs (Kubachyna O., 2011).

Other key factors in determining a high level of competitiveness are high barriers to exit and elevated fixed costs that characterize the industry. Beside sunk costs that companies sustain over the time, which constitute an obstacle for firms in the industry to exit the business, other obstacles are long-term labor, material purchasing and leasing contracts (Blanc L., 2014).

## 5. Orphan drug current market dynamics

The size of the global ODs market has increased significantly in recent years. Total sales exceeded USD 96.6 billion in 2013 and top 20 OD companies for sales shared 68.3% of the entire market (USD 66 billion) the same year (EvaluatePharma, 2014).




*(Source: Data elaboration from EvaluatePharma, 2014)*

Indeed, there has been a significant increase in the number of ODs available to treat rare diseases, mostly driven by renewed pharmaceutical industry efforts to address the unmet needs in orphan diseases, encouraged by incentives promoted by the regulatory agencies. In addition, the saturation of the markets for diseases with large patient populations, such as asthma, diabetes and hypertension, has oriented the pharmaceutical industry towards refocusing R&D efforts on more specialist, niche diseases where the unmet need is more significant and the barriers to entry much lower.

Assessing the market size for ODs is complicated by the fact that some of the products that have orphan designation could, conceivably, no longer be considered true orphan drugs as they have gone on to expand their labels to include non-orphan diseases. A key example of this is Roche's Rituxan/MabThera (rituximab) which has been approved for

several rare diseases, such as B-cell chronic lymphocytic leukaemia, Wegener's granulomatosis (WG) and microscopic polyangytiis (MPA) and is therefore considered to be an OD. However, it is also approved for the treatment of certain diseases with significant patient populations, such as rheumatoid arthritis, and was the third highest selling drug worldwide in 2013, with revenue of $8.9 billion (Philippidis A., 2014).

There are several other limitations which affect the accurate sizing of the ODs market. First of all, there are variations in the classifications and requirements for ODs across countries. In addition, some products gain orphan status, are granted approval and then removed from the OD database at the request of the developer.

Recent estimates have valued the global ODs market at $82.6 billion for 2011 and $86 billion in 2012 (Burns M., 2013). This is primarily due to key blockbuster ODs, such as Rituxan (rituximab) and Glivec (imatinib) that generate billions of dollars in annual sales as shown in Table 2.

**Tab. 2 - Top ten orphan drugs in terms of annual global sales, 2013**

| Product | Company | 2013 sales (million USD) |
|---|---|---|
| **Rituxan (rituximab)** | Roche | 5,954 |
| **Glivec (imatinib)** | Novartis | 4,693 |
| **Copaxone (glatiramer acetate)** | Teva/Sanofi | 4,328 |
| **Revlimid (lenalidomide)** | Celgene | 4,280 |
| **Avonex (interferon beta)** | Biogen Idec | 3,005 |
| **Alimta (pemetrexed)** | Eli Lilly | 2,703 |
| **Rebif (interferon beta)** | Merck KGaG/Pfizer | 2,334 |
| **Velcade (bortezomib)** | J&J/Takeda | 2,526 |
| **Advate (factor VIII)** | Baxter | 2,234 |
| **NovoSeven (eptacog alfa)** | Novo Nordisk | 1,556 |

*(Source: Company annual reports, 2013)*

Large pharmaceutical companies all have significant OD interests. As table 3 shows, several of the top global pharmaceutical companies derive a significant proportion of their sales from ODs. The importance of ODs to the commercial success of leading pharmaceutical manufacturers further demonstrates the trend to shift away from big primary care blockbuster products and towards specialist products. This has enabled portfolio diversification as well as a lower general risk for pharmaceutical companies.

Indeed, ODs are rarely refused reimbursement or funding and successfully developing one helps to guarantee a revenue stream, albeit for a limited patient population (FirstWord, 2014).

The issue of pricing in ODs is still a topic of debate as high cost of developing ODs that only serve a small percentage of the population has to be attributed somewhere. However, for patients suffering with rare disease, there is the issue of expensive and limited treatment options. Indeed, the demand for therapeutic drugs is "price inelastic": increasing the price does not reduce how much the drugs are used (FirstWord, 2014).

**Tab. 3 - Top 10 companies by orphan drug sales, 2013 - Rank Company Global Sales**

| Rank | Company | Global Sales (billion USD) |
|---|---|---|
| **1** | Novartis | $ 11.3 |
| **2** | Roche | $ 9.5 |
| **3** | Celgene | $ 5.7 |
| **4** | Pfizer | $ 5.3 |
| **5** | Teva | $ 5.1 |
| **6** | Bayer | $ 4.2 |
| **7** | Sanofi | $ 3.3 |
| **8** | Baxter International | $ 3.3 |
| **9** | Biogen Idec | $ 3.0 |
| **10** | Eli Lilly | $ 3.0 |

*(Source: EvaluatePharma, 2014)*

Notwithstanding lower average R&D cost per OD if compared to non-orphan due to the worldwide authorities' incentives for health and biotechnology industries, the final price of the product is much higher for four main reasons (Hornby C., 2014).

*1) Drug development costs needs to be recovered*. Pharmaceutical companies will invest analogous amount of money in developing an OD as they would on developing a drug which can potentially treat thousands of people. They will still need to recoup that investment, and with fewer potential patients, the cost per patient will rise (Hornby C., 2014).

*2) The "need" for payers and insurers to pay the high costs*. OD companies can generally set high prices in part because insurance companies and payers will pay for them. Insurers generally follow the principle of medical necessity, and as the symptoms of many rare diseases are very severe it is hard for them to argue that treatment is not necessary. Furthermore, they use to pay a lot of money for palliative medicine for patients suffering from a rare disease, so if a new drug is marketed which can offer concrete advantages then this might represent a more cost-effective option. Finally, refusing to cover the cost of treatment for a rare disease patient will result in terrible publicity (Hornby C., 2014).

*3) The lack of competition* due to the ODs marketing exclusivity that limits patients' choice (Hornby C., 2014).

*4) The assistance (beyond insurers) available to rare disease patients to help cover costs*. For uninsured patients, there are often options available to assist with high ODs costs. Moreover, patient advocacy groups are also very involved in securing treatment for patients in need of assistance. On the other hand, OD developers need to compensate the high costs they charge at least in the public opinion, and one way is by offering free or discounted drugs for some patients. For example, Genzyme provided approximately $103 million in ODs for free in 2013 (Hornby C., 2014).

In conclusion, having a lower R&D cost for Phase III trials (which is based on an average of 35.367 patients versus 497.013 patients for non-orphans) and a higher final price, the ODs expected return is almost double than non-ODs (14.9% vs 8%), thus making it a very attractive market. In particular, 20% of total R&D expenses in the pharma industry are dedicated to OD investments though creating 32% of the total value in the industry (EvaluatePharma, 2014).

## 6. Corporate Social Responsibility and strategic Corporate Social Responsibility

Definition of Corporate Social Responsibility (CSR) varied over times. One of the earliest definitions was the one given by Howard Rothman Bowen. In 1953, Bowen wrote: "A business decision maker has an obligation to make those decisions and follow those lines of action that protect and enhance society's interests beyond just serving his/her own business interest". Much later, in 1970, Milton Friedman wrote his well known article on the New York Times Magazine where asserted that ''there is one and only one social responsibility of business: to use its resources and engage in activities designed to increase its profits so long as it stays within the rules of the game, which is to say, engages in open and free competition without deception or fraud'' (Friedman M., 1970). This definition in turn received many criticisms. One of the key criticisms was his assumption that CSR activities result at the expense of corporate financial performance.

More recently, Dahlsrud analyzed 37 definitions of CSR. His study helps in understanding the meaning and the role of CSR in modern era. In his paper, CSR definitions were considered following three steps. First, they were gathered through a literature review. Second, using a content analysis of the definition, different dimensions of CSR were identified (stakeholder, social, economic, voluntariness and environmental). Third, the frequency of all the definitions referring to a specific dimension was evaluated through Google search and the usage of each dimension was estimated (Dahlsrud A., 2006). The stakeholder and social dimensions were the most used, followed by economic dimension and finally voluntariness and environmental dimensions. Most used definition considering Google's frequency count was the one given by the Commission of the European Communities in 2001: "A concept whereby companies integrate social and environmental concerns in their business operations and in their interaction with their stakeholders on a voluntary basis" (CEC, 2001). Second most used, was the one formulated in occasion of the World Business Congress for sustainable development in 1998: "The commitment of business to contribute to sustainable economic development, working with employees, their families, the local community and society at large to improve their quality of life" (WBCSD, 1998).

However, a model of CSR that seem to fit in the most specific way to the ODs market is the Schwartz and Carroll's three-domain model, formulated in 2003. According to the authors, CSR of a company can be defined considering three different domains: economic, legal, and ethical. Different domains outline how responsibility of business in society includes the simultaneous consideration of a profit motive, compliance with laws and regulations and moral obligations that should guide good corporate feats (Schwartz M. S., 2003). In particular, the *Economic domain* includes all the activities which are intended to have either a direct or indirect positive economic impact. The *Legal domain* refers to the firm's reactivity to legal expectations of the society according to the country jurisdictions. Finally, the *Ethical domain* refers to the ethical responsibilities of business as perceived by the general population and stakeholders (Schwartz M.S., 2003). A Three-Domain approach is a framework that helps firms primarily on focusing how they align and integrate their economic, legal, and ethical actions with their core business activities in order to derive economic and non-economic benefits. Among non-economic benefits reputation enhancement or the use of CSR to recruit and motivate high quality workers are highly considered (Schwartz M.S., 2003).

The concept of 'strategic CSR' has been introduced as a complementary framework by and Porter and Kramer in 2006. According to them, CSR is not necessarily intended as a cost for the company. If approached strategically in fact, it may generate opportunity, innovation, and competitive advantages for corporations, while solving pressing social problems (Porter M.E., 2006).

An example of strategic CSR is offered by Toyota. The company, in response to public concern about pollutants, developed the hybrid-engine Prius. The Prius has not only significantly reduced auto emissions, but it also gave Toyota a clear lead over other motor companies in hybrid technology (Porter M.E., 2006).

There are two approaches to define strategic CSR. The first refers on socially responsible activities being integrated with the core business activities of a firm. The second refers to outcomes of CSR activities in terms of profit maximizing and achieving sustainable competitive advantage. This can be obtained in different ways such as developing for example "green products" appreciated by consumers aware of the

environment or performing the "cause-related marketing" where a firm will make a philanthropic contribution for every purchase made by consumers (Porter M.E., 2006).

Several criteria permit to evaluate if a firm uses its CSR strategically. The three most relevant strategic attributes are centrality, specificity, and visibility (Bruyaka O., 2013).

*Centrality* consider how CSR activities are aligned with the overall strategy of the firm. An example of a great centrality is a firm dedicated to OD development having a program of helping low-income patients with rare diseases. On the opposite, the same initiative undertaken for altruistic reasons by another firm not involved in ODs development would have a lower centrality. *Specificity* refers to the direct benefits that the firm may obtain as compared to those that the society may obtain. In the case of OD development, specific legislation guarantees some benefits and incentives to any company that obtains an OD designation. Finally, *visibility* is related to the enhancement of the firm's reputation as a result of the CSR activities. For this reason, strategic CSR initiatives should have high visibility and be widely known using appropriate communication strategies (Bruyaka O., 2013).

### 6.1. Orphan Drugs and Corporate Social Responsibility

Biopharmaceutical companies are commonly criticized for reasons including excessive profit levels, high price fixing, unethical drug development, and limited patient access to life saving/extending drugs. Thus, companies deriving their profits from health, need to do business in accordance with CSR principles. In this view, the ODs represents a peculiar context to be studied (Bruyaka O., 2013).

In order to clarify what drives CSR activity in OD development and the extent to which US and European companies strategically use their CSR activities in this field, Bruyaka and coworkers performed a research study published in 2013.

From 2010 to 2012, these Authors conducted a series of interviews to 20 executive managers from 9 biopharmaceutical companies in the US and the EU using a semi-structured questionnaire developed according to the three-domain model of CSR (Schwartz M.E., 2003) and integrated with the concept of strategic CSR according to Burke and Logsdon (1996) and Porter and Kramer (2006). For the purpose of their

study, these authors integrated data collected from the interviews with publically available secondary data (e.g. official video, press releases, industry publications, etc.) on CSR activities of other firms in the pharmaceutical industry. Finally, to illustrate the principle of visibility, interviews were complemented with a quantitative study of 100 biopharmaceutical firms' websites. According to the Authors, the firms' sample of this study represents a variety of business models as it is composed of small and large firms, and firms specialized in ODs together with firms peripherally involved in ODs through diversification (Bruyaka O., 2013).

As an example, publically available data from Novartis and Pfizer websites on CSR and ODs are reported.

**From Novartis' website** (Novartis, 2014)

*Question*: By definition, a rare disease affects just a small fraction of the population — fewer than 200,000 persons in the United States and fewer than 1 in 2,000 in Europe. Why does Novartis work on diseases that affect so few individuals?

*Novartis*: "It's not a business decision. We follow the science and evaluate the unmet medical need when selecting projects, which often leads us to rare diseases. We typically focus on a specific molecular pathway, develop a compound that impacts the pathway, and then ask, 'Which diseases are associated with dysregulation of the pathway?' It's very exciting to be working for a company that encourages you to go after a disease that makes sense, even if the potential market isn't big."

*Question*: Why does the science often lead you to rare diseases?

*Novartis*: "Some rare diseases have uniform underlying causes, with defects in a single molecular pathway to blame. Common diseases, on the other hand, tend to be more heterogeneous and mechanistically complex, with multiple pathways involved. If we test our drug in a rare disease with a single defective pathway, then we can see if it works as intended before expanding to common diseases where the pathway is one of multiple variables."

*Question*: You mentioned that unmet medical need factors into project selection at Novartis. Can you elaborate on that in relation to rare diseases?

*Novartis*: "Rare diseases were historically overlooked by pharmaceutical companies, and many of them still aren't understood. There are relatively few approved treatments for them. We'd like to expand the therapeutic arsenal for doctors to use in helping patients. We concentrate on rare diseases that are debilitating where the scientific understanding is strong and where we believe new treatments could significantly improve the lives of patients with these diseases."

*Question*: Is there a danger of overpromising?

*Novartis*: "We have to be extremely careful not to overpromise. If it's a devastating disease without an approved therapy, patients and their families get very excited about the prospect of a treatment. It's important for us to convey the clinical research process, including the long timelines involved, and to make sure that patients understand there's no guarantee that an experimental treatment will work. We can partner with patient advocacy groups — which frequently encourage participation in clinical trials — to help set expectations that match reality."

*Question*: How has Novartis adapted clinical trials to address the needs of patients with rare diseases?

*Novartis*: "Instead of asking patients with a rare disease to visit a separate contract research organization site to participate in a clinical trial, we work to integrate the research into their regular care. We find the experts in a particular disease, clinicians who may or may not have experience in clinical research, and we provide them with infrastructure and training to set up a study site."

*Question*: What else can be done to facilitate clinical trials in rare diseases?

*Novartis*: "We need to do a much better job of characterizing the natural history of these diseases so that we can measure whether or not new treatments are working. Take McCune-Albright syndrome, the disease I encountered at Mass. General. The underlying cause of the syndrome was discovered in 1991, but we still have not found a treatment. If we did have a specific therapy, we would still need more information to figure out how to run a clinical trial. We don't always know how quickly the average patient with a particular rare disease gets worse, making it difficult for us to determine if an experimental treatment is slowing the rate of progression. To run an effective clinical trial, we must be able to score success."

**From Pfizer's website** (Pfizer, n.d.)

"Pfizer's Rare Disease Research Unit (RDRU), led by Chief Scientific Officer Kevin Lee, is adopting an innovative and collaborative approach to the development of new medicines whereby it looks to develop strategic partnerships with academic and commercial enterprises to create novel therapeutics across the spectrum of rare diseases. Our commitment to academic collaboration is highlighted by the recent signing of the Rare Disease Consortium agreement with six of the leading Universities in the UK, providing a vehicle to work collaboratively with leading physician scientists on drug discovery projects. We are looking to capitalize on recent scientific advances linking diseases to specific genetic defects. As 70% of rare diseases are monogenic in origin, we believe this is an area where scientific knowledge is enabling significant advances in drug development. Our expertise in large molecule therapeutics, small molecule protein chaperones, and transcriptional modulators has resulted in a broad pipeline of potentially transformative medicines across multiple disease area."

Results of the questionnaire following the three-domain model of CSR according to Schwartz and Carroll (2003) depict the relationship between this theoretical model and actual practices.

Concerning the economic domain of CSR, main results of the study showed that the pharma companies perceive the ODs market as a business opportunity, that developing

ODs in niche markets helps in avoiding competition and that developing ODs implies working on innovations given that little knowledge exists on rare diseases (Bruyaka O., 2013).

From a legal point of view, OD legislation can be considered as a 'positive' control as it encourages ethical and social activities as a result of market failure to do so without government support (Bruyaka O., 2013). Study interviews showed that companies consider OD legislation to improve economic attractiveness of this activity as well as help justify ethical initiatives. One example of this combination is a biopharmaceutical firm giving its ODs to patients for free as a result of an agreement between the firm and the government, as happened in the case of Alexion and the French government (Bruyaka O., 2013). Finally, according to an ethical point of view, results showed that many biopharmaceutical firms consider that being involved in OD development "automatically" implies ethical responsibilities (Bruyaka O., 2013).

Overall, this study illustrates the different reasons that motivate biopharmaceutical firms' involvement in OD. Certain companies moved in the ODs market mostly for economic reasons with the aim to develop and commercialize relevant innovations. At the same time, small size firms more often dedicate their work to cure rare diseases following an ethical issue. These small companies are usually founded to find a therapy for a rare disease from which their founder's loved ones suffer (Bruyaka O., 2013). These small size firms, both in US and EU, consider big pharmaceutical companies diversifying into OD as moved by economic opportunism without having the right approach required to invest in this field. Nevertheless, most of pharma companies believe that to successfully do business in rare diseases ethical responsibilities need to be addressed. Moreover, because of the specific economic conditions (e.g., small market size, few and geographically distant physicians and patients, etc.), companies have to interact directly with patients, doctors, and pharmacists. This personal interaction give them a greater sense of moral responsibility (Bruyaka O., 2013).

Moreover, all of the firms participating in the study acknowledged that economic, legal, and ethical motives are usually gathered, and none of them taken alone is sufficient to motivate involvement in ODs. In fact, economic attractiveness of OD market (economic domain) is a result of OD legislation (legal domain). On the other hand, ethical motives

alone (ethical domain) will not help to grant the firms' mission to cure patients with rare diseases as far as otherwise they will go out of business (Bruyaka O., 2013).

According to interviewed companies, main obstacles encountered by companies in entering the ODs market are referred to legal incentives provided by the OD legislation not being enough to trigger research on treatments for rare diseases. These mainly include: getting the OD designation in US does not imply a favorable treatment by FDA (from 1983-2012 only 403 out of 2,641 drugs that received the designation were approved), grants are too small to cover expenses, costs and rigor requirements on trials on ODs are hindering, the threshold of rare diseases should be recalculated in US as the population grows (this is done automatically in EU), and finally a common procedure is needed in EU in order to simplify research on and commercialization of ODs (Bruyaka O., 2013).

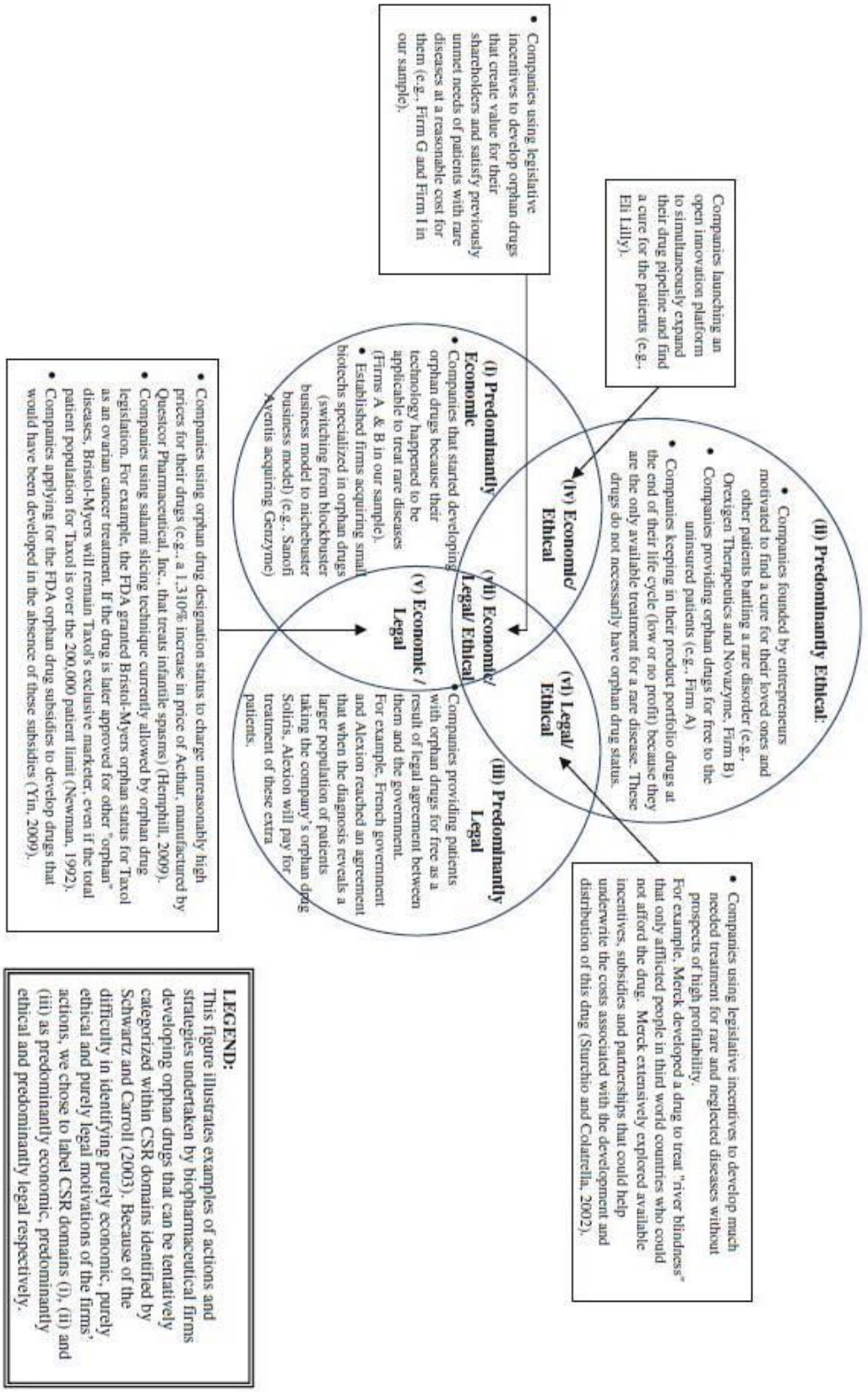
Evaluation of strategic attributes of CSR revealed different conditions among large and small/medium size companies. About *centrality*, the study showed that while developing ODs is a core strategy for many of the small companies involved in this activity, large pharmaceutical companies focused on common diseases only recently. About *specificity*, that refers to the ability of a firm to capture some benefits of the program for itself rather than for the society in general, this is more focused by large companies. Firms may gain a stronger reputation from producing social benefits, mostly derived from recognition by patients and associations of the firms' efforts going in that direction. An example of specificity is the one given by Eli Lilly. The company developed an innovative platform to identify molecules that will help in treating multi-drug resistant tuberculosis. Even if results will benefit the whole society, Eli Lilly gained a pole position at the centre of scientific research and will keep intellectual right on future discoveries (Bruyaka O., 2013).

Specificity is therefore strongly linked to *visibility*. Visibility analysis showed that small/medium-sized companies are less active in publicizing their involvement in CSR activities on their websites when compared to the large ones (26 % vs 79%). These are also less active in treating of ethical, social or philanthropic topics on their communication channels. An explanation might be connected to the fact that often it is not clear to small/medium companies the relevance of visibility or they are not able to

correctly communicate or finally, that they cannot afford a large-scale communication (Bruyaka O., 2013).

Despite several limitations related to the limited sample size and to the nature of the 'self-presentation' of the companies, this study demonstrated the usefulness of the concept of strategic CSR, in helping critically understand the activities of biopharmaceutical firms with respect to OD development (Bruyaka O., 2013).

Fig.1 summarizes results of Bruyaka et al. study



## 7. An insight on Chiesi Farmaceutici S.p.A.

Chiesi Farmaceutici S.p.A. was founded in 1935 in Parma, Italy, by Giacomo Chiesi. G. Chiesi founded the company through the acquisition of Laboratorio Farmaceutico Parmense with the aim of doing research and develop drugs needed in Europe.

The factory was destroyed during a bombing raid in the World War II and later rebuilt once the war was over. Expansion into international markets begun in 1966 when Giacomo Chiesi's sons, Dott. Alberto and Dott. Paolo, started to manage the company without ever stopping. Nowadays, the company exports its products in more than 70 countries and it is directly present in 26 (Chiesi Group, n.d.).

Chiesi had a steady and strong growth over the years becoming one of the largest pharmaceutical companies in Italy and making his entrance in the top 50 in the world for revenue (Chiesi Report, 2015).

To better understand the size of the company as of 2014 more than 4100 workers are employed, 236 million have been invested in R&D (about 20% of the total revenue) and as the annual report states, the revenue has been over euro 1.34 billion with a net income of euro 192 million for 2014 fiscal year (Chiesi Report, 2015).

Over the last five years, the company became involved in the ODs' market as well. Strategically, reasons that led the company to this decision include:

- High unmet medical need: only 500 treatments for over 7000 rare diseases.
- High level of incentives given: e.g. clinical, financial.
- Low level of competition: competition is limited by exclusivity granted by authorities, little knowledge of disease pathophysiology, difficulties in finding effective mechanism of action, very few patients, difficulties creating generic drugs and large number of diseases without treatment.
- Close relationship with patients: important continuous exchange of information with them which allows to improve patient satisfaction by fitting the treatment to patient needs.

- Sustainable business model: Higher prices if compared to non-orphan drugs allow companies to recover the investment and encourage them to focus attention on a very rare population.

For what concern the allocation of financial resources between orphan and non-orphan drugs investment projects everything depends on the different existing opportunities. Projects' approval follows a multi-level process that strongly consider the allocation of human resources.

Among the most important ODs in the company's portfolio figure: Peyona, Glybera, Holoclar and Lamazym. Each of them can provide an example of a different strategy used by Chiesi Farmaceutici S.p.A. to enter the ODs' market:

**Internal Development Process**

Peyona is used for the treatment of primary apnea (the cessation of breathing for more than 20 seconds) in preterm neonates. Primary apnea is due to the baby's breathing centres in the brain not being fully developed while the active substance in Peyona, caffeine citrate, is a stimulant of the nervous system, which reduces the effect of adenosine, stimulating the brain to resume breathing (EMA, 2015). This drug has been developed from "scratch" by Chiesi Farmaceutici S.p.A.. Indeed, this drug has been discovered, developed, tested and now manufactured and commercialized entirely internally by the company.

**License Agreement**

Rights over an OD as Glybera, instead, have been acquired through a license purchase. This OD in fact, has been developed by the Amsterdam-based company UniQure and just marketed and commercialized in selected markets through a license purchase by Chiesi Farmaceutici S.p.A. for EUR 17 million in collaboration financing and EUR 14 million in equity financing (which also included a co-development in a hemophilia B therapy).

Chiesi will have exclusive rights for the commercialization of Glybera and the therapy in Europe and other selected markets (Brazil, Mexico, Pakistan, Turkey, Russia, Commonwealth of Independent States, plus China only for Glybera) and will also

financially support the remaining development costs for the program of UniQure for hemophilia B.

On the other hand, UniQure will retain commercial rights in the United States, Japan and some parts of Latin America, Asia and Australasia. The Dutch company will also receive royalties of 20-30% to the net sales of the product (Tekeste A., 2013).

This OD is the first and only approved gene therapy in Europe and US and it is used to treat adults with lipoprotein lipase deficiency, an orphan disease that results in abnormally large particles of fat in the blood and causes inflammation of the pancreas (Spain L., 2012; UniQure, n.d.).

**Partnership with University or Academia**

Holoclar, the first stem-cell cure in the world approved by the EU and the US, is an OD manufactured by Holostem Terapie Avanzate (Holostem Advanced Therapies) – a spin-off of the University of Modena and Reggio Emilia – at the Centre for Regenerative Medicine "Stefano Ferrari" (CMR) of the same University.

In case of patients with a loss of the corneal epithelium, often related to workplace injuries (caused, for example, by burnt lime, solvents or acids), domestic accidents (for example eye burns caused in adults and children by detergents or abrasive agents) or in the cases of assault with chemical agents, this OD permits to regenerate and restore its functions. Holoclar, precisely – "looks like a kind of contact lens, it is transplanted into the patient and allows to obtain a long-term transparent cornea and a full recovery of visual acuity, without causing any rejection reaction, because it consists of cells of the patient him/herself." says Professor Graziella Pellegrini, Coordinator of cell therapy at CMR and director of R&D and co-founder of Holostem (Chiesi Group, 2015).

Holoclar approval was included by the EMA in the most important achievements in the last 20 years and represents a pioneering approach to entirely new sectors in medicine, which provide therapeutic solutions for serious health problems that until recently represented unmet medical needs. The product is expected to be launched in 2016 in some EU countries.

**Company Purchase (through acquisition)**

Lastly, Lamazym has been added to Chiesi's portfolio through the purchase of the Danish pharma company Zymenex Holding A/S by Chiesi UK; financial terms of the contract were not disclosed. This Phase III OD is indicated for alpha-mannosidosis, a genetic disease that causes a progressive deterioration of the central nervous system. With this acquisition, two compounds in pre-clinical development for other ultra-rare indications were acquired as well (Chiesi Group, 2014).

The acquisition also resulted in a consolidation of Chiesi Farmaceutici S.p.A. presence in the special care area, thanks to the incorporation of Zymenex R&D department into its own R&D organization. The CEO Ugo Di Francesco stated that: "Expanding R&D's activity and know-how, we believe that we will be able to successfully commercialize new and in development drugs in order to increase our portfolio, expand our international presence and strengthen our competitive position." (AboutPharma, 2013).

All these strategies, however, have an underlying process in common, that is followed by the company in order to make his decision over the development or the acquisition of an OD (through any of the four model described previously) that can be summarized as it follows. The phases intertwine with each other and the importance of each differs case by case:

1) STRATEGIC FIT: The first phase consists in a strategic analysis of the OD investment project. In fact, several factors (e.g. the medical target) are evaluated to test the consistency of the introduction of the OD in the company's portfolio with his own strategy. Some previously established guidelines needs to be followed in order to approve/refuse the investment project for an OD. One of the most important factors in the decision is the "unmet medical need". It is fundamental for Chiesi in the decision process the presence of this element which is defined by the European Commission as "a condition for which there exists no satisfactory method of diagnosis, prevention or treatment authorized in the Community or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected." (EC, 2006).

2) SCIENTIFIC RATIO: The scientific rationale is “a reason, based on supporting scientific evidence, that a particular action is chosen” (Anderson D.M., 2009). In order to prove it, several factors are taken into account such as literature and outcomes of other therapies for the specific rare disease and other similar diseases and previous recorded experiences about it. This phase is so delicate, usually due to the lack of information about epidemiology, diagnostic, animal models and patients, that highly reduce the successful rate of proposed OD investment projects.

3) ECONOMIC AND FINANCIAL ANALYSIS: The last phase consist in the verification of the economic feasibility and convenience. The principal project evaluation method applied by the company is the Net Present Value (NPV) calculated through an analysis of different scenarios. The company use the Weighted Average Cost of Capital (WACC) to discount the expected cash flows where the main variables, price, competition, launch date (unexpected delays are frequent) and drugs specifications determine the different scenarios. NPV, even for a good OD investment project, is usually lower than an average non-orphan drug one. Also important is the calculation of the Internal Rate of Return (IRR) of the project, which instead might be higher if compared to a non-orphan drug investment project in some cases. Come last the Payback Period evaluation model, in which different cut-off period are set for different projects.

For Chiesi Farmaceutici S.p.A. entrance and investments in the OD market are based on both ethical and economic grounds, in 2014 in fact, the group established a venture capital firm focused on the area of rare and orphan disorders. Ethical grounds, indeed, often overcome the uncertainty, risks and lower returns (in absolute terms) for the company in that kind of investment. “We believe that rare diseases accord us a great opportunity to create a path worthy and beneficial to society. Society realizes the drama of rare diseases. Chiesi Ventures want to be instrumental in funding great research and development opportunities for therapies that can provide a hope for the patients and their families.” is what states Chiesi Ventures’ website (Chiesi Ventures, n.d.).

OD in fact are also an important element of Corporate Social Responsibility for Chiesi: every year the company organizes the Rare Diseases Day: an internal communication campaign created to sensitize about this theme (Chiesi Report, 2015).

Beside rare disease and ODs, the strong social commitment of the company is inherent in its mission and Values. Company's CSR concerns four main aspects (Chiesi Group, n.d.):

- Ethics: adopting a Code of Ethics and Conduct and the Chiesi Group Guidelines on Ethics and Compliance drafted to harmonise the process for the adoption of the Code of Ethics and Conduct by the other affiliates of the group.
- Environment and Security: though the implementation of the Environmental Management System ISO 14001 and the Safety Management System Certificate OHSAS 18001 standards.
- Chiesi Foundation Onlus: a non-profit organization founded in 2005 involved in three main areas of activity: scientific research, education and international cooperation. Events and initiatives organized and supported by the Foundation include Respiration Day, aiming at increase awareness about respiratory diseases and its prevention, together with the support of scientific research projects focused on the fields of pulmonology and neonatology and international cooperation initiatives with the aim to improve neonatal care in less-developed countries.
- Donations and contributions: devolved to Italian patient associations and with particular attention to the needs of the territory and the community in which the company operates.

The company is strongly committed in turning CSR into concrete actions. This translate into environmental protection, safety programs and numerous initiatives towards employees, specific patient categories and local communities also. Through these initiatives, the company's goal is to help socially and economically disadvantaged people in need and encourage safe and 'green' behaviors.

Among initiatives dedicated to employees, EUR 11.5 million have been invested in training and development in order to enhance workers' organizational and professional skills (Chiesi Report, 2015).

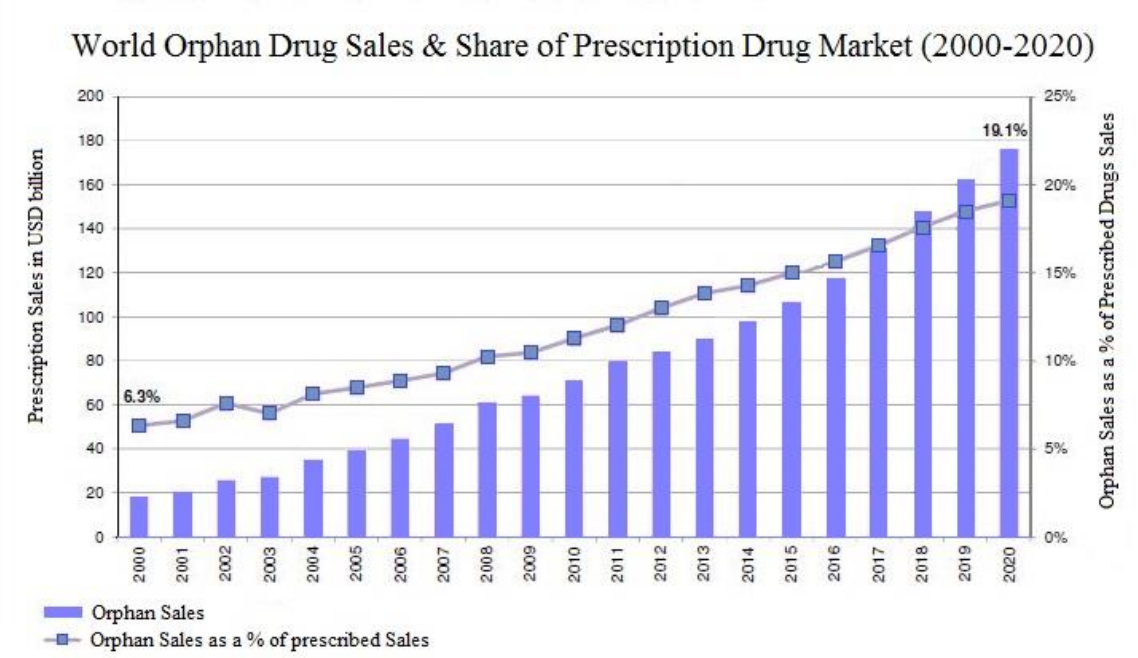
From a geographical standpoint, company's CSR activities are distributed on the different countries in which it operates supporting no-profit organizations in many of them. Several anti-corruption measures have been put in place as an anti-corruption legislation as well as the intervention of external audits. Other international activities are carried out through the International Cooperation area of the Chiesi Foundation.

Energy, water consumption and $CO_2$ emission are constantly measured and have been on a positive trend of reduction from 2013 (Chiesi Report, 2015).

This focus on Chiesi Farmaceutici S.p.A. provides a practical insight on how the company successfully deal and manage with the OD market and its commitment devolved into this field for its important social impact. In addition, it is possible to better understand how some companies engaged in ODs development perceive their involvement as a responsible business activity beyond the economic dimension.

## 8. Which possible future scenarios for orphan drugs?

The number of emerging ODs is expected to increase. This rise will not just be due to greater numbers of diseases being researched but also much larger, more prevalent diseases becoming segmented into groups of smaller, orphan diseases. In 2013 total ODs' market was valued USD 96.6 billion. Growing at a six year compound annual growth rate of 10.5%, ODs' total market value forecast to reach USD 176 billion by 2020 as reported in a study conducted by EvaluatePharma. It has been also estimated that 19.1% of worldwide prescription sales will consist in ODs by 2020 (EvaluatePharma, 2014).




*(Source: EvaluatePharma, 2014)*

The 'orphanization trend' will strongly influences treatment of rare disorders, however payers worry about the side effect this trend will have on the total healthcare expenditure, especially since newer ODs are becoming more expensive over the time. Example of high price ODs include, Soliris commercialized by Alexion Pharmaceuticals' at more than USD 500,000 per year per patient for paroxysmal nocturnal hemoglobinuria (Equities, 2014) and Advate sold by Baxter International for almost USD 450,000 per year per patient. (EvaluatePharma, 2014).

Therefore, payers at all levels (national, regional and local) would aim to restrict access to certain ODs because of the the growing number and the higher prices. In certain

countries HTA assessments (Health technology assessment: a "systematic evaluation of the properties and effects of health technology taking into account social, economic, organizational and ethical issues") may start to be applied to ODs to help important decisions as the pricing or reimbursement of the drug. For other countries as in the US is also expected a higher involvement by the government in pricing decisions and approval process through the draft of guidelines and recommendations for companies. Payers, usually health insurance companies, feel powerless in this regard (FirstWord, 2014).

These considerations make market access for ODs more and more challenging and possible future scenarios arise for companies and policy maker.

### 8.1. Future scenarios for companies

In order to sustain the growth of the ODs' industry is fundamental a system renovation coordinated with a restoration of trust between stakeholders (Surani F., 2013).

Feasible solutions in this direction include:

1) The industry is expected to experience an increase in risk share schemes among pharmaceutical companies, patients and payers, in order to justify the high price, increase efficiency and to reduce concern over costs and risky investments. Various drug markets have already in place risk share schemes, in particular those where drugs cost-benefit are considered not enough to be reimbursed. These schemes and agreements can be very different one to the other. Certain schemes are structured that the company bear the risk of the drug functioning, that results in paying back the drug cost to the patient if some minimum requirements are not met. Other arrangements are characterized by the offer of the first cycle of a drug for free, subsequent further cycles rebated and then entirely paid once expected benefits are delivered. These schemes might be necessary to be implemented in the ODs market to manage and to cope with the price-increasing trend of orphan products (FirstWord, 2014).

2) Trust among payers and other stakeholders in the ODs market needs to be repaired and renewed. Not only benefit delivered are usually not enough to justify the expensiveness of a certain drug, but also often payers feel that some pharma companies are unethically taking advantage of the ODs designation in order to charge inflated prices only to gain extra-profit. Moreover, one of the hardest controversies that biopharma and healthcare companies face is to explain and provide reasons and grounds for producing and selling an expensive orphan drug based on a modified already existing therapy that has been changed only to make the drug fall into the OD definition. The example reported by a BBC article "A GP's view: Orphan drug costs prohibitive" is oral ibuprofen, which costs about GBP 0.08 per gram. However, the drug exists also in the OD market in an intravenous form (Pedea, commercialized by Orphan Europe) for the treatment of the rare disease patent ductus arteriosus sold for GBP 6,575 per gram (BBC, 2013). Orphan Europe, justified the higher price for its drug explaining that it was specially developed for that specific orphan disease and therefore it should not be compared to ordinary oral ibuprofen without taking into consideration the whole process (BBC, 2013). Following Pedea, Firdapse, has been approved in the EU as an orphan drug in 2009 for the rare disease of Lambert-Eaton myasthenic syndrome. However, as reported on a study published in the Orphanet Journal of Rare Diseases in 2012 the expensive Firdapsde drug is only a slightly modified version of an unlicensed and inexpensive drug that has been available for many years already (Hughes-Wilson W., 2012). Firdapse's price was between 50 and 70% higher than the generic unlicensed compound (BBC, 2013). As a consequence, some physicians wrote an open letter to UK prime minister, published in the British Medical Journal, complaining companies who were unethically using OD legislation to support their own advantage (Nicholl D., 2011). The debate between BioMarin, the manufacturer, and the authors of the letter continued until the lead author wrote an FP10 prescription for the less expensive base drug, 3.4-diaminopyridine (Nicholl D., 2011; MacDonald V. 2010). Although BioMarin then voluntarily cut its prices for Firdapse by 10%, the UK commissioners network did not allow further funding of the drug and stated that although legally Firdapse and 3.4 diaminopyridine were two separate entities, the two forms of the drug could be considered equivalent. Comparing costs of the two forms, the base form of the drug

would have cost GBP 1200 per patient per year, while Firdapse would have cost, on average, GBP 44,000 per patient per year (Nicholl D., 2011).

For this reason pharma industry, through the collection and disclosure of ODs data, needs to create a transparent engagement with patients and governments. Pharma companies should talk to payers and patients to understand their needs, to communicate the potential impact of the drug and to initiate an open dialogue that will benefit all stakeholders. In turn, governments should support companies with funding and convenient regulation (FirstWord, 2014).

3) Some payers suggest that an involvement in pricing decision would be necessary. While industry stakeholders argue that return on investment (ROI) makes high prices necessary, greater transparency is needed as to how prices are determined. It is widely believed that pharmaceutical companies will still make profits if prices are lowered. Therefore, an open discussion on how initial prices for some rare disease drugs are calculated, and what is the methodology followed, is highly desirable. For example, there should be a higher awareness over the R&D and drug pricing process followed by pharma companies, as quite often population is not aware that the launch price of a drug includes also the cost of previously failed projects (Surani F., 2013). Major challenge in OD development is a lack of diseases' pathophysiology knowledge that would enable to organize beneficial and cost-effective R&D programs. Early engagement and coordination among patients, regulatory agencies, policy makers and industry may therefore reduce the uncertainty faced by the whole system. Collaboration is also necessary to balance investors' return while decreasing drugs' sale prices. Moreover, a discussion with regulatory agencies in advance, before starting the investment project, may help in finding possible solutions to lower the risk at both sides. To accept price deductions if a drug isn't as effective after commercialization or, at a certain point after launch, to lower prices as other drugs become available could be some examples. On the other hand, if reluctance from EU payers to reimburse high-priced ODs continues, there is a risk the industry will stop investment in this sector (Surani F., 2013).

### 8.2. Future scenarios for policy makers

In general, pharma companies are criticized by governments for lack of investment into a new range of medicines that fulfill rare medical needs. Governments in turn reward innovations hugely and assume a more active role in directing R&D priorities. Therefore, it is important for pharmaceutical companies to enter into agreements with governments (FirstWord, 2014).

Authorities however, in supporting pharma industries should not only offer financial aid but also help in increasing awareness of the importance of OD development among patients and stakeholders, highlighting the direct effects of OD development on patients' wellness, but also the long-term benefits for society in terms of technology development.

Indeed, the development of new technologies is an important issue that moves firms into ODs market. Focusing this as a benefit to the entire society from a politic point of view, governments simultaneously allow firms to strength their strategic CSR profile.

Finally, another way to support companies may be acknowledging those that significantly contribute in improving the treatment of rare diseases. As an example, in US, the National Organization for Rare Disorders (NORD) usually give prestigious governmental awards to companies reaching fundamental achievements in the area of OD development (NORD, 2011).

## 9. Conclusions

Over the time an increasing number of large pharma companies are focusing on the OD market, attracted by its grow rate, above average returns and the rising awareness about this topic. In the past, only small and specialised biotech companies were involved in ODs, often selling their compounds to larger firms able to bear commercialization costs later. Governments and regulatory agencies through incentives and dedicated policies play a fundamental role in the expected strong grow. Otherwise, in fact, it would not be financially viable and convenient for companies to develop and commercialize ODs. Indeed, limited consumer's market and a small and disperse patient's population to study make the initial investment difficult to recover and the evidence for the safety and effectiveness of ODs hard to find.

However, stakeholder often critics the ODs' industry. They argue that companies are taking advantage of the incentivized system in order to gain above-normal profits and that those countries where universal healthcare is provided, especially in this period of budget reductions, cannot deal with such extremely high prices in the long term. Therefore, is important to find the right balance in incentives provided and ensure that company do not unethically take advantage of them in order to gain extra-profit.

In addition, is very important to redefine pricing approaches employed by companies and in general ensure that customers and patients are aware of how a specific price is determined. Moreover, more data and outcomes need to be disclosed by companies as payers are becoming more reluctant and want proof of what they are paying for, especially in case of extremely expensive drugs and treatments that have limited clinical benefit or are not disease modifying.

In this scenario, CSR plays a crucial contribution for companies who invest in ODs. As of today, companies often have a twofold advantage in engaging in ODs' activities. On one hand, it represents a possibility of growth for the company as the market itself expands. Moreover, to invest in ODs often generate internal knowledge spill-over, increase in expertise and know how that to a certain degree can be applied to other non-orphan related productions.

On the other hand, from a strategic CSR standpoint, dealing with ODs, firms are seen as concerned and involved in 'ethical issues' that returns in terms of public relations and goodwill.

ODs market analysis showed, however, that the latter advantage is often not being fully exploited by companies since ODs' activities are not always joined with an appropriate communication strategy. In this view, managerial experience should be improved and knowledge about the strategic use of CSR more deeply understood to gain proper visibility when firms are involved in ethical issues. An example of appropriate use of CSR emerges by the insight on the Chiesi Farmaceutici.

To conclude, ODs represent a complex and delicate trade off which will increasingly rely on cost-benefit analysis as ODs are becoming more expensive and orphan diseases are growing in terms of numbers ("orphanization" trend). Patient needs are significant and an optic of a future were ODs are not reimbursed and therefore produced would be unreasonable, as it would be inadequate and unacceptable for both payers and drug developers. However, cost-benefit analysis cutoffs will vary over the time as population's perception and economic resources available change.

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