



Department of Business & Management

Chair in Corporate Strategies

Strategic Product Portfolio Management:
A Focus on the Bio-Pharmaceutical Sector and Roche

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*Un ringraziamento speciale ai miei genitori e mia sorella
che mi sostengono e quotidianamente mi trasmettono
la sicurezza che la vita sarà ricca di numerosi altri traguardi.*

A loro e a tutti coloro che hanno contribuito a questo successo va il mio più sentito ringraziamento.

E' Proibito

È proibito piangere senza imparare,
svegliarti la mattina senza sapere che fare
avere paura dei tuoi ricordi.

È proibito non sorridere ai problemi,
non lottare per quello in cui credi
e desistere, per paura.
Non cercare di trasformare i tuoi sogni in realtà.

È proibito abbandonare i tuoi amici,
non cercare di comprendere coloro che ti stanno accanto
e chiamarli solo quando ne hai bisogno.

È proibito non essere te stesso davanti alla gente,
fingere davanti alle persone che non ti interessano,
essere gentile solo con chi si ricorda di te,
dimenticare tutti coloro che ti amano.

È proibito non fare le cose per te stesso,
avere paura della vita e dei suoi compromessi,
non vivere ogni giorno come se fosse il tuo ultimo respiro.

È proibito non cercare di comprendere le persone,
pensare che le loro vite valgano meno della tua,
non credere che ciascuno tenga il proprio cammino
nelle proprie mani.

È proibito non creare la tua storia,
non avere neanche un momento per la gente che ha bisogno di te,
non comprendere che ciò che la vita ti dona,
allo stesso modo te lo può togliere.

È proibito non cercare la tua felicità,
non vivere la tua vita pensando positivo,
non pensare che possiamo solo migliorare,
non sentire che, senza di te,
questo mondo non sarebbe lo stesso.
non sentire che, senza di te, questo mondo non sarebbe lo stesso.

Alfredo Cuervo Barrero

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Introduction

The pharmaceutical industry is continuously changing and innovating; over the last decade industry leaders have broadened their portfolios and strengthened their balance sheets in the run up to loss of exclusivity (LoE) of their blockbusters. Indeed, companies in this sector have to navigate in an increasingly volatile environment given by the combination of finite patent life, long drug development cycles with high probabilities of failure at every step, the high costs associated with the development and launch together with the post launch market risks. In this respect the efficient management of strategic products portfolio is the necessary condition for long-term survival, thus playing an pivotal role for every company that aims at maintaining its competitive advantage and increasing value for all its stakeholders. Portfolio management – the dynamic decision process, whereby new product projects are constantly evaluated, selected and prioritized – thus is significant in the decision-making process for allocating resources, because it is guided by principles that maximize value, balance components on a number of different parameters, firm’s financial goals, corporate strategy and risk tolerance profile, assuring that any modification represent a strategic fit as determined by a risk-benefit analysis.

Starting from a comprehensive overview the life science industry and its contribution to national economies and healthcare system, the first chapter aims at defining the playing field in which *Big Pharma* compete, highlighting both the micro and macro environmental factors that shape the industry and impact the value creation process. It then focuses the attention to the pharmaceutical and biotech businesses and explains how recent challenges are transforming the traditional pharma business model and how can be leverage to succeed in the new evolving healthcare landscape. Opportunities and challenges are indeed defining a new business environment, eventually determining the evolution towards what has been defined *Pharma 2020*. In the face of challenges in their business environment pharmaceutical companies are being forced to try and reinvent themselves. Only the firms willing to change their corporate strategies, readapting their current products portfolio by choosing the “best jams” will have long-term success. In fact, the key to long-term success lies in building a balanced heterogeneous portfolio. Pharma companies must constantly keep an eye on their portfolios, allocating the right amount of resources to valuable candidates. Even though the paramount goal is clear, there is no defined path to reach it and the route each company have taken depends exclusively on their individual aims and circumstances.

The second chapter therefore intents to deep dive on common growth strategies that have been employed as external sources of innovation to expand firms’ product portfolios, making sure R&D pipelines are well-prepared to replace blockbusters’ soon-to-be-lost earnings in order to maintain the industry historically high-growth rates. As a response to the current market challenges, *Big Pharma* have re-evaluated their corporate strategies, engaging in a variety of external growth strategies – such as M&A, strategic alliances and licensing

agreements. The chapter aims at highlighting the main rationales as well as analysing the main portfolio deals that have occurred in recent years. As business environment continues to evolve, pressures from the payers continue to increase and the costs and risks to develop innovative drugs continue to surge, companies must pursue the strategic alternatives they deem necessary to increasing their productivity and maintain their leadership positions.

While doing this companies need to perform strong portfolio management to improve their product pipelines and target areas where they can discover novel medicines in unmet need therapeutic areas. Thus the chapter aims also at reviewing the commonly used techniques and matrices in terms of portfolio analysis employed to inform firms about their own competitive position suggest strategic options and define priorities in terms of resource allocation among the different products or business. Furthermore, it aims at outline how a bulletproof PM process should be structured and at investigates the importance of having in place a sound portfolio management process, able to lead to effective strategic decision-making in order to carefully maintain a balanced heterogeneous R&D pipeline and product portfolio; whenever the firm's portfolio is judged unbalanced the firm may either grow capabilities in-house leveraging on its internal R&D to generate the next blockbusters or more frequently rely on external growth strategies to shorten the time-to-market.

The last chapter wants to move the attention on Hoffman-La Roche – a worldwide leading research-focused healthcare group. In particular, the chapter emphasizes its innovation-driven strategy and explains how portfolio management within the pharmaceutical division is managed within such multinational corporation. It analyzes how the resource allocation and compound selection in late-stage development process work at the headquarter level. At the same time it outlines an exercise of product prioritization that periodically takes place within each Group's affiliate.

In conclusion the thesis directs the reader's attention to a current business challenge faced by pharmaceutical companies, including Roche: the undertaking of the biosimilars in the EU market and how this threat or opportunity may drive – and has already driven – changes in firms' strategic portfolios through portfolio deals. With this respect it aims at underlining strategic responses against biosimilars that pharma companies can undertake, while pointing out what is pathway Roche has embarked on. In line with its business strategy and long-term objectives, Roche's innovation-based strategy with its focus towards areas of highly unmet needs, will continue to fuel its growth. Its portfolio strategy emphasises the attention on optimizing its businesses by improving the current standard of care as well as on expanding the portfolio through differentiated medicines, by concentrating in new therapeutic disease areas, outside its comfort zone – oncology.

1 The Life Sciences Industry

This first chapter aims at introducing the life science industry by describing how it has become a key asset for national economies as well as society at large. It will focus on the bio-pharmaceutical sector, emphasizing the dynamics that characterize it, while highlighting opportunities, threats and critical success factors.

1.1 The Healthcare Industry: an Overview.

“The pharmaceutical industry is comprised of companies engaged in research, development, manufacturing and marketing activities of drugs and biologics for human and veterinary use¹”.

The pharmaceutical industry is defined as the business of developing, manufacturing, marketing and selling drugs. It differentiates itself by a high degree of complexity; by extend risks associated in particular to the core business activity, R&D, by the need to achieve high economies of scale and scope in order to absorb the R&D costs and by the remarkable margins to be earned. Nevertheless, firms within this sector are subjected to strict regulation concerning patents, clinical trials and promotion as well as control on the pharmaceuticals’ efficacy and safety². This complex regulation is explained by the positive social and economic impacts this sector has, which play an important rationale in allocating resources to the healthcare sector. In fact, in many developed countries the national healthcare systems are in charge of sustaining healthcare costs as well as granting accessibility to medicines for all patients in need. It is because of this reason that sometimes governments, who represent the main buyer, intervene in the market to lower prices and introduce reimbursement policies aiming at limiting the growing expenditure in healthcare.

The industry directly supports innovative advances in medicines, it is therefore of great value to patients in need, but also to the healthcare system and society as whole. The pharmaceutical industry is not only a key asset to scientific and medical progress but also to the economy as it stands out for its significant positive economic impact.

¹ As defined by the Census Bureau. International Trade Administration (July, 2010)

² Gianfrate F., *Economia del settore farmaceutico*, Il Mulino, 2004.

1.1.1 The Pharmaceutical Industry: An Asset to Medical Progress and the Healthcare System.

“The innovative pharmaceutical industry is driven by, and drives, medical progress” (EFPIA, 2016, p.2); each year thanks to intense R&D processes and advances both in sciences and technology, this researched-based industry contributes to significant improvements in patients well being, such that today’s people can expect to live longer than they did a century ago. Only in the decade between 2000-2009 it was estimated an improvement in population weighted mean life expectancy at birth of 1.74 years, from 74.25 to 76, across 30 OECD countries and that innovative medicines have contributed to 73% of this improvement.³ Major steps in biopharmaceutical research have allowed not only an increase in life expectancy but also a reduction in mortality rates and today’s medicines offer new promising prospects that range from personalized medicine to harnessing the power of *Big Data*.

In addition to changing lives, innovative medicines play a key role in reducing all indirect healthcare costs associated to disease progression. Indeed medicines help healthcare systems to be sustainable by reducing costs in other parts of the system, such as hospitalizations, surgical procedure as well as even compliance to medicines⁴, yielding health gains and cost savings. Lichtenberg (2009) estimated that the per capita spending on cardiovascular hospitalizations would have been 70% higher in 2004 had new medicines not been introduced in the market during the period 1995-2004⁵. Surprisingly the cost of some disease could even bankrupt the entire system had medicines not existed to at least shift the paradigm from curing to preventing.

1.1.2 The Pharmaceutical Industry: A Key Asset to the Economy

Despite its complexity, this sector is a critical pillar for the economy and represents a vital part of a broader dynamic ecosystem with a high impact multiplier: by providing capital investments it supports demand for innovation through R&D, it generates opportunities and it stimulates many intertwined supply chain activities, such that each gain and loss can have an outsized effect on the economy as a whole. The biopharmaceutical industry, in fact, makes a significant contribution to the European economy, first and foremost in terms of

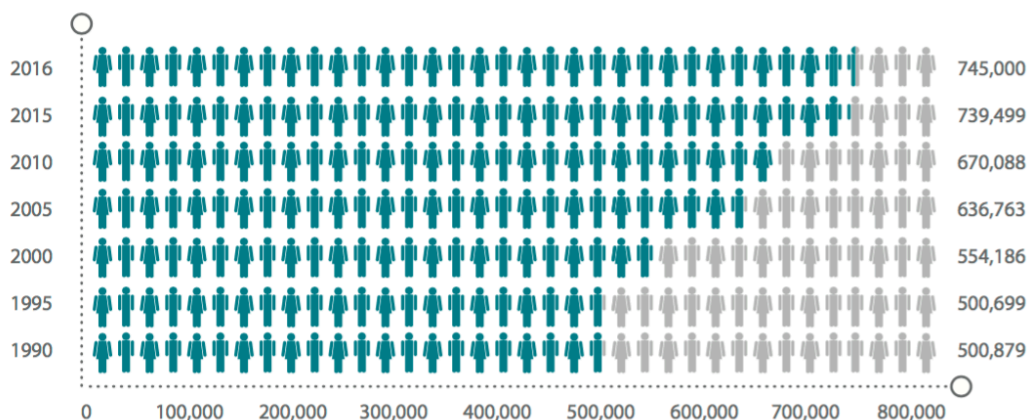
³ Lichtenberg, F.R., *Pharmaceutical Innovation and Longevity Growth in 30 Developing OECD and High-Income Countries, 2000-2009*, Health Policy and Technology, 2012.

⁴ PhRMA, *2012 Profile Pharmaceutical Industry*, April 2012.

⁵ Lichtenberg, F. R., *Have newer cardiovascular drugs reduced hospitalization? Evidence from longitudinal country-level data on 20 OECD countries, 1995–2003*. Health Econ., Vol.18. pp. 519–534, 2009.

employment. It is, indeed, one of Europe’s major high-tech industrial employers, hiring directly some 725,000 people and generating three to four times employment indirectly both upstream and downstream. Furthermore a part of these are valuable skilled jobs, one out of 6 are highly skilled R&D position, which should help maintaining a high-level knowledge and preventing further brain drain in EU (Figure 1).

Figure 1 The Industry Contribution to Employment



Source: EFPIA, 2017

On the other hand this sector benefits worldwide economies as it generates one of the highest trade surplus among the high technology sectors, only in 2013 it is estimated to have reached 75 Bn Euros⁶. This seems to indicate, as EFPIA claims, that the industry can even “restore Europe to growth and ensuring future competitiveness in an advancing global economy” (EFPIA, 2017, p. 4) and it is categorized as the industry that adds the most value to the economy per employee - pharmaceutical employees are generating 80% more value per employee than other industries⁷.

The Battelle analysis estimates that the positive economic contributions go beyond the impact of the biopharmaceutical industry on direct jobs, in fact for every dollar in output generated another 1.40\$ in output is produced in other sectors. Especially in the U.S. the biopharmaceutical sector is “well recognized as a dynamic and innovative business sector [that] generates high quality jobs and powers economic output and exports for the U.S. economy⁸” (PhRMA, 2012, p.14), (Figure 3).

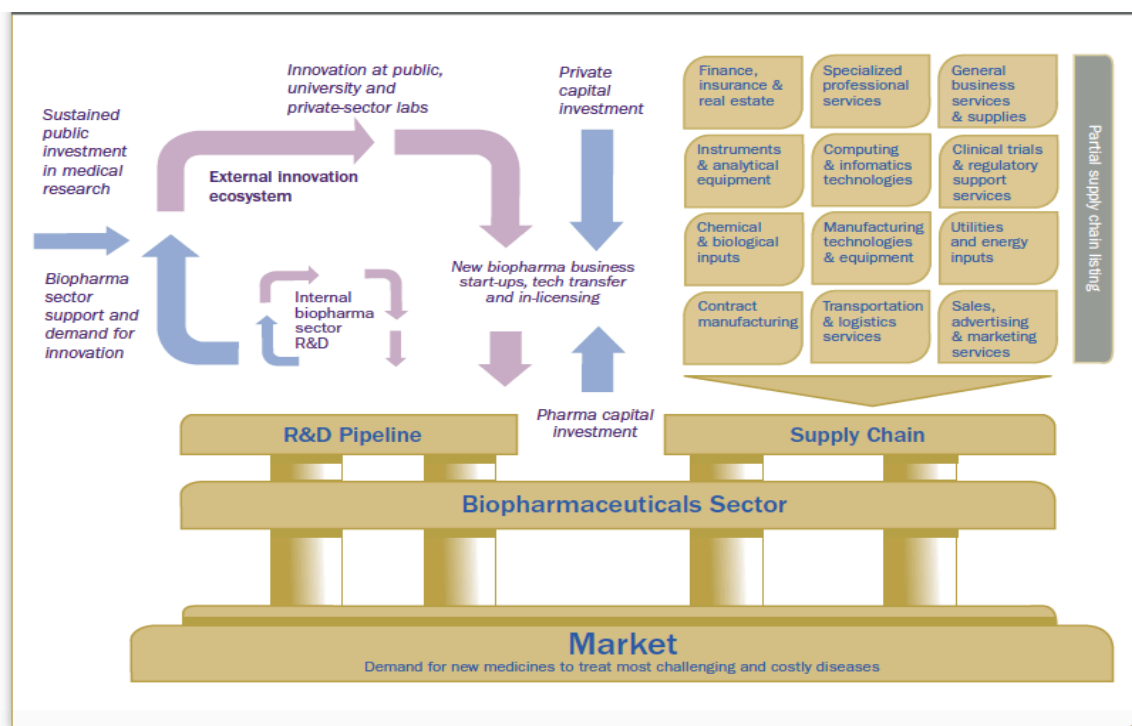
⁶ Eurostat, COMEXT database, April 2016; Pharmaceutical Industry Figures, EFPIA, 2015.

⁷ Health Advances analysis; EU industrial R&D Investment Scoreboard, 2015; Eurostat database.

⁸ As cited from the Battelle Technology Partnership Practice, *The U.S. Biopharmaceuticals Sector: Economic Contribution of the Nation*, Battelle Memorial Institute, July 2011.

By investing more of its revenue in generating new knowledge through R&D the biopharmaceutical sector is the second largest funder of research and development in Europe with a 19% share in 2014. Companies in this sector have undeniably invested substantial amount of money in R&D worldwide in order to bring to the market the most innovative therapies, in particular for chronic and deadly diseases. It is estimated that since 2006 over \$1,100bn was invested in R&D and that in the next four coming years another \$900bn will be disbursed⁹. These investments in innovation translate into significant societal value as development in the pharmaceutical sector is strongly targeted at societal disease priorities such that patients are able to continue contributing to the community.

Figure 2 The Biopharmaceutical Sector and its Role in the Business Ecosystem



Source: Battelle Technology Partnership Practice, 2011 prepared for the Pharmaceutical Research and Manufacturers of America.

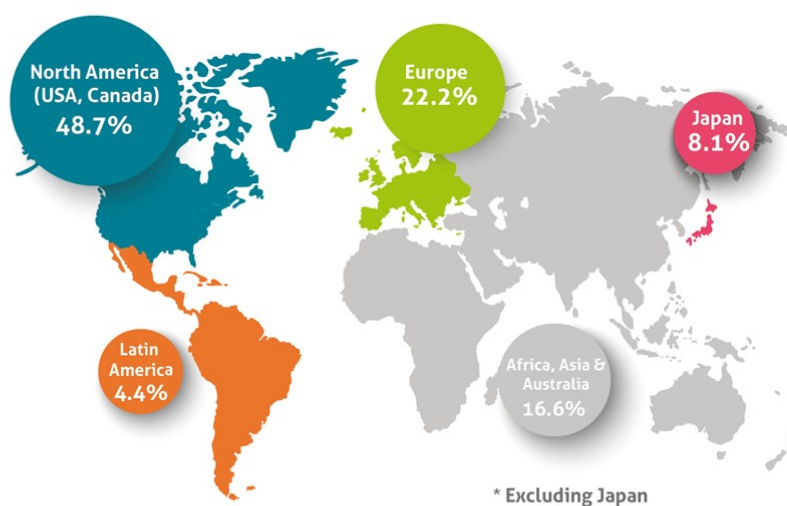
Nevertheless, even if opportunities for sustained and continuous innovation in the market are significant, so are the challenges: the escalating costs associated to R&D despite productivity declining, regulatory hurdles, tougher global market condition together with intense competition as well as the impact of fiscal austerity measures introduced in Europe since 2010 and harsher price policies.

⁹ EvaluatePharma, *World Preview 2016, Outlook to 2022*, 9th Edition, September 2016.

1.1.3 The Industry in Numbers

The overall global industry¹⁰ has experienced a fairly strong growth over the period 2007-2011, reaching total revenues equal to \$1,107 billion in 2011 thus exhibiting a compound annual growth rate (CAGR) of 6.7% between the same period¹¹. In 2015 the world pharmaceutical market was worth approximately €715,9 billion at ex-factory price¹². If those sales are breakdown by geographic area it can be noticed how USA and Canada continue to have world's largest share at 48.7%, followed by Europe and Japan (Figure 2).

Figure 3 World Pharmaceutical Market's Breakdowns by Geographic Area¹³ - 2015 Sales



Note: Europe includes Turkey, Russia and Ukraine

Source: IMS Health (MIDAS), May 2016; EFPIA, 2017.

EvaluatePharma (2016) estimates that the prescription drugs sales are forecasted to grow at 6.3% per year (CAGR) reaching \$1.12 trillion in 2022 (Figure 4). The core engine behind this growing trend is the new wave of innovative treatments approved by regulators in the last years, especially in the context of orphan drugs. This demonstrates how R&D activities are more oriented towards narrower patients populations characterized by large unmet need and easier market access. Nevertheless, even though the outlook towards 2020 does seem

¹⁰ It comprises of global pharmaceuticals, biotechnology and life science tools and services market.

¹¹ MarketLine, *Industry Profile: Global Pharmaceuticals, Biotechnology & Life Sciences*, September 2012.

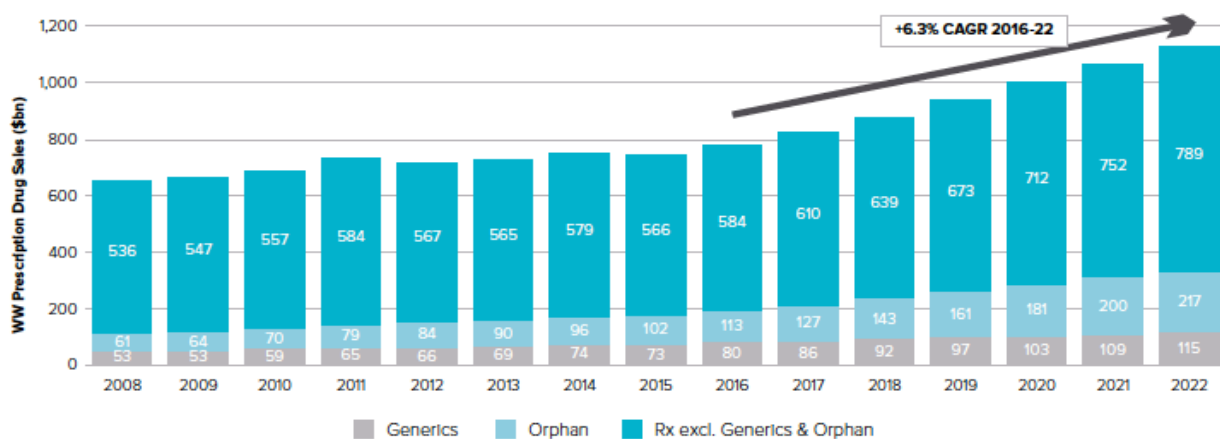
¹² EFPIA, *The Pharmaceutical Industry in Figures: Key Data 2016*, June 2016.

¹³ Data relate to global retail and hospital pharma market at ex-factory prices.

promising and confirms a positive growing trend the pharma industry must still be vigilant for sales at risk due to the imminent patent cliff era ahead in which top biologic blockbusters will be challenged by biosimilars.

Over the last decade there has been an escalating demand for medicines and global spending is expected to exceed \$1,400Bn by 2021. The outlook for medicine spending through 2021 is for growth to settle down to a more steady level of 4–7% CAGR over the next five years, lowering the increasingly high rates witnessed in 2014 and 2015 (Figure 5). Indeed if present trends are any guide global spending could be worth even more: world population is increasing, with an estimate of 7.6 billion by 2020¹⁴, aging and there is an increasing prevalence of chronic disease, all of which are burdening healthcare systems, leading to a greater demand for care. Next year’s growth “will be driven primarily by new medicines in developed markets and increased volume in pharmerging markets. The number of new medicines reaching patients will be historically large, addressing significant unmet needs, [...] these areas of significant innovation are expected to drive most global spending growth, particularly in developed markets, but will be a key focus of payers and constrained by cost and access controls as well as a greater focus on assessments of value” (QuintilesIMS, 2016, p.1).

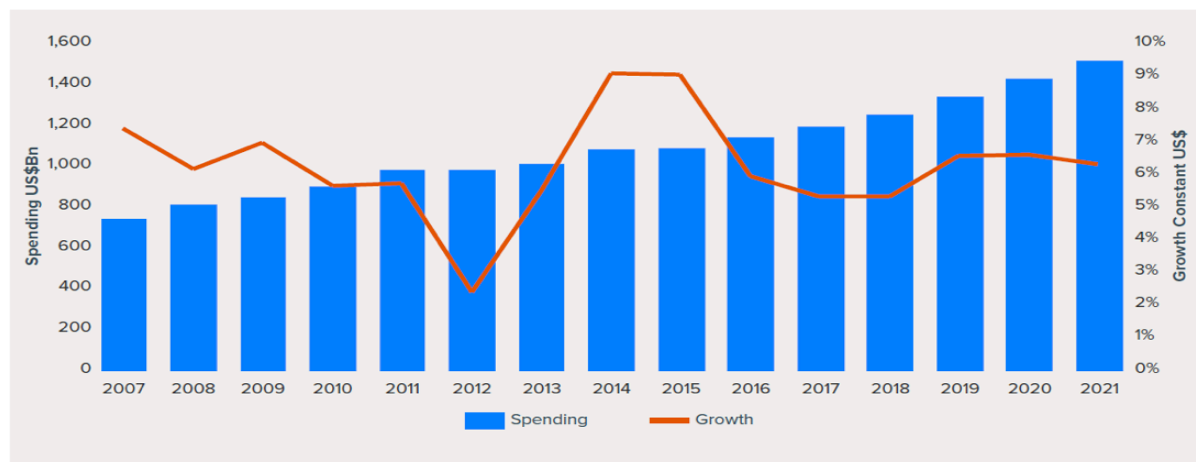
Figure 4 Worldwide Prescription Drugs Sales (2008-2022)



Source: EvaluatePharma, 2016

¹⁴ Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat, World Population Prospects: The 2010 Revision, <http://esa.un.org/unpd/wpp/index.htm>

Figure 5 Global Market Spending and Growth 2007-2021



Source: IMS Market Prognosis, Sept. 2016; QuintilesIMS Institute, Oct. 2016.

Furthermore global spending will continue to rise, as the pharmerging markets¹⁵ will contribute a greater share of spending driven by an increasing affordability of basic medicines due to rising incomes. As income will continue to rise based on macroeconomic expansion, government-sponsored programs will also continue to foster access to medicines, limiting patients’ exposure to costs and encouraging greater use of medicines. PwC also supports this claim and forecasted that sales in 2020 will be mainly attributable to growth markets¹⁶, which will reach approximately 30% of sales - more than doubling the EU5 countries, as these economies are improving access to healthcare and more people will gain access to basic medicines. Indeed, developed markets are forecasted to contribute less to the global spending because of a large period of patent expiry that will lower brands spending in those markets. The loss of exclusivity of blockbuster brands between 2014 and 2015 resulted in a reduction of brand spending of \$14.2Bn¹⁷. Nonetheless the impact of those patent expiries in U.S. “while higher in absolute dollars in the next five year, will be lower in percentage contribution [in fact] U.S. spending on medicines is forecast to reach \$610-640 billion in 2020 on an invoice price basis, with steady mid-single digit growth driven by innovation and offset by loss of exclusivity”. (IMS Institute, April 2016, p.5)

Contribution to worldwide spending will also come from increasing generics expenditure, both from increasing utilization of existing generic products and new ones. Generics have already taken a larger share of total global

¹⁵ Pharmerging countries are defined as those with >\$1Bn absolute spending growth over 2012-16 and which have GDP per capita of less than \$25,000 at purchasing power parity (PPP). Pharmerging markets include China, Brazil, India, Russia, Mexico, Turkey, Poland, Venezuela, Argentina, Indonesia, South Africa, Thailand, Romania, Egypt, Ukraine, Pakistan and Vietnam.

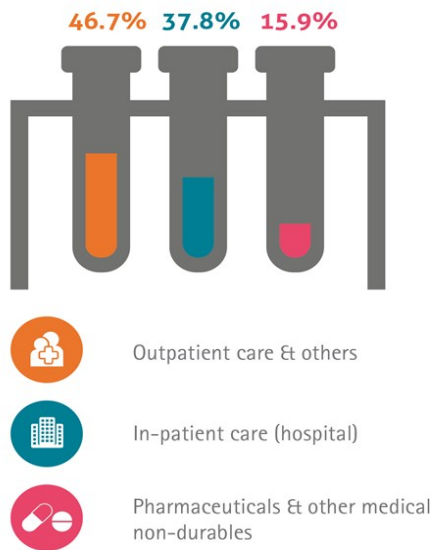
¹⁶ Growth markets include BRIC countries (Brazil, China, India and Russia) as well as Mexico, Turkey, Poland, Venezuela, Argentina, Indonesia, South Africa, Thailand, Romania, Egypt, Ukraine, Pakistan and Vietnam.

¹⁷ QuintilesIMS, *Price Declines after Branded Medicines Lose Exclusivity in the U.S.*, January 2016.

medicine spending, increasing from 27% in 2012 to an estimated 36% by 2017¹⁸. Indeed the global generic market will continue to rise as payers pursue cost containment objectives, since generics have the advantage of a lower cost, but also because blockbuster drugs are approaching patent expiry.

Especially during the last few years there has been intense debate around the affordability challenges faced by the healthcare systems, across all Europe, even though there has been an increase healthcare demand. When medicines' spending is put in context, it is observable that this account for less than one fifth of the total healthcare expenditure in Europe¹⁹, on average 15.9% is spent on pharmaceuticals and other medical non-durables while the majority of costs accounting for outpatient care and in-patient care (Figure 6).

Figure 6 Breakdown of the Total Health Expenditure in Europe



Source: OECD Health Statistics 2016, May 2016; EPFIA Calculations

Therefore when spending on medicines is put in perspective, these represents only a small share of the total healthcare spending. Nevertheless, expenditures on total healthcare²⁰ today are growing faster than growth in the pharmaceuticals expenditures such that expenditure on hospital care ranges from three to six times the total spending on prescription medicines, reaching 5.7 in USA. However, “medicines are often the principal focus of cost containment policies, rather than government understanding an analysis of the entire healthcare spend [...]

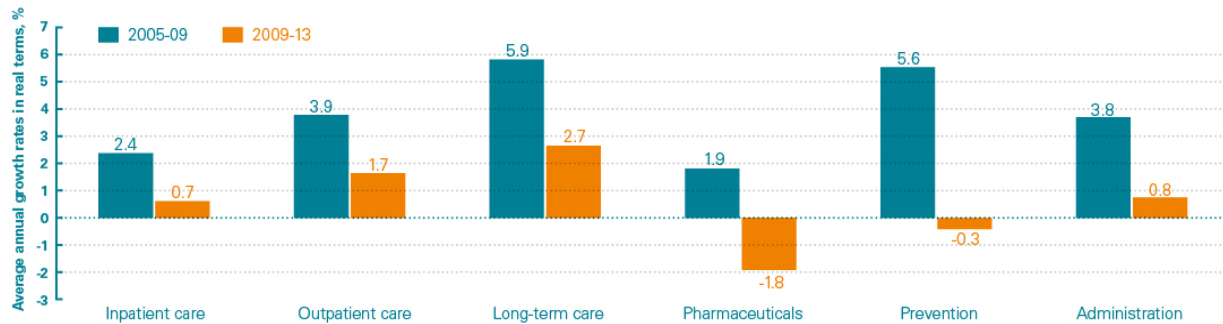
¹⁸ Deloitte, *2016 Global Life Sciences outlook: Moving forward with cautious optimism*, 2015.

¹⁹ EPFIA, *Annual Report 2015: From innovation to outcomes*, June 2015.

²⁰ Total healthcare spend includes costs such as hospital care, physician/clinical services, nursing home care etc.

(but) the reality is that since 2009 spending on medicines in OECD countries has fallen by an average of 1.8% per year” (EPFIA, 2015, p.6) (Figure 7).

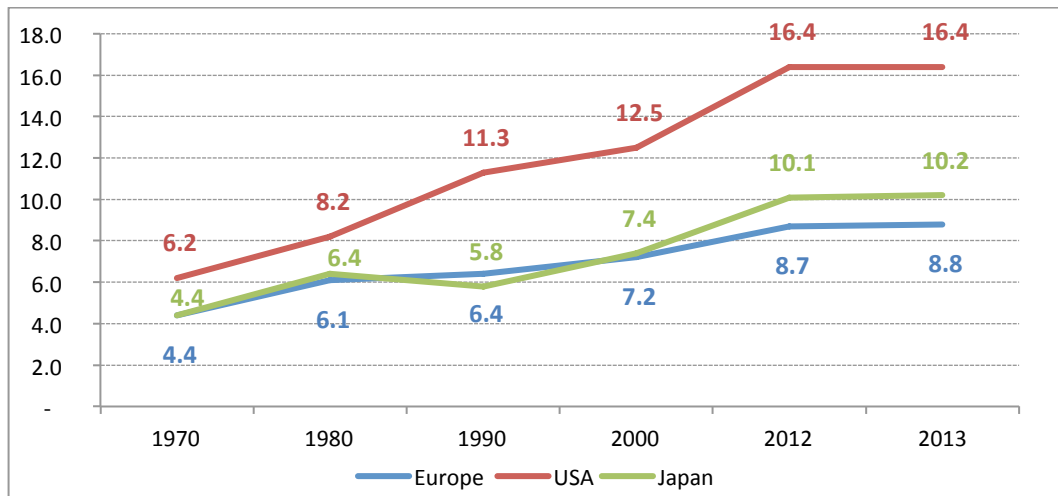
Figure 7 Medicines Costs in Context: Total Health Expenditure vs. Medicines Expenditure



Source: OECD Health at Glance, 2015.

Soaring healthcare costs are a serious hurdle facing all the stakeholders in the industry and healthcare expenditures as a percentage of gross domestic product (GDP) is climbing in every country at every income bracket (Figure 8), even though it's rising more steeply in mature markets where the industry has historically made most of its money. It does seem like this trend is unsustainable and indeed governments are trying to contain costs in this sector, limiting the growing spending to a level they feel appropriate by pressuring stakeholders to share the burden. The only way to reverse this trend – according to PwC – is to alter the concept of healthcare itself; instead of focusing on treatments we need to focus on preventing diseases.

Figure 8 Healthcare Total Spending²¹ as % of GDP



Source: Elaborated from OECD Health Data 2015, May 2016.

1.2 Market Characteristics and Structure

Understanding the Pharmaceutical industry is the starting point to properly pinpoint the playing field in which the *Big Pharma* companies compete and understand where the whole market is headed. For this reason it is important to bear in mind what is the extended framework in which pharmaceutical firms operate, that is to analyse both the macro and the micro-environmental factors that contribute at shaping the industry as well as the forces at play impacting value creation.

1.2.1 PEST Analysis

When analysing the macro environmental factors influencing this industry, political, economic, technological and social factors (PEST analysis) must be taken into consideration. From a political point of view there has been a growing pressure of national governments on pricing due to limitation on available resources to funds the soaring healthcare costs in order to balance the high costs of medications and the sustainability of the

²¹ Spending both public and private.

overall system. This has created a difficult situation for major pharmaceutical corporations, which have to manage regulations from different governments. Furthermore debates on patents – especially now that blockbuster drugs are approaching expiry – fuels political pressures on how to manage incentives and healthcare cost containment actions powers generics importance since they have a cost advantage. A large problem companies face is also the legal costs of doing business, as they often spend millions to file for patent infringement lawsuits and in lobbying activities in order to ensure a quicker approval process for drugs to enter the market and strengthening intellectual property rights (IPRs) protections.

As previously highlighted, the pharmaceutical industry is a key asset to global economy due to its significant positive impacts and spill over effects. Despite the fact that pharmaceutical market will be facing challenges in the near future, due to patent expirations and cost containment legislations, the overall state of the healthcare and pharmaceutical industry will still be positive, showing how profitable the industry has become over time. Nevertheless, pharmaceutical companies are struggling to maintain growth and profitability as margins decrease²². Now more than ever emerging markets are considered growth driver, shifting geographic priorities for the industry; in these developing countries, national GDP is growing and demographics show that the standard of living is raising, implying that there is more readily available income, which results in more consumption and economic support.

Technology represents indeed an important key factor to success as the industry is boosted by constant innovation in drug research. Additionally technology is becoming more and more embedded into companies' business models. The pharmaceutical industry has seen a steady increase in the funding of R&D and it is by far one of the largest funder²³. Even though costs keep rising, so does breakthroughs in the fields of pharmaceuticals; however R&D spending is not always synonym of productivity and indeed the number of original new drug approvals has rather stable in recent years. As a direct consequence a global wave of partnership with biotech ventures, which backed companies with efficient R&D, started to take place and product pipelines are turning to specialized product targeted at rare complex diseases which can demand higher prices. With technology advancing and revenues increasing, a push for mass globalization has taken place. With more consumers having access to healthcare, the industry will still gain value and grow.

When considering the business environment in which pharmaceutical companies operate, it does not go unnoticed how the industry has become more patients-centric and the fact that patients are becoming

²² Arthur D. Little, *Trends in the Pharmaceutical Industry*, January 2016.

²³ See par. 1.1.2

increasingly better informed and powerful is leading all the stakeholders to change their approach and pharma companies to search for novel business model beyond the blockbusters, offering services beyond the pill.

In the pharmaceutical sector, the institutional framework has a pivotal role in influencing firms' strategies, which must act in the quest for legitimacy. Indeed a company is only legitimate if it behaves following codes established by the organizational field²⁴ and as they deviate from the field they are not seen as legitimate anymore they are sanctioned by the surrounding environment. Pharmaceutical companies therefore rationally pursue their interests within their institutional environment, considering both the formal and informal level of constraints. Two pillars comprise the institutional environment:

- **Regulatory Pillar** – formal institutions, which regulate the information asymmetries between the patients and the pharmaceutical companies by exercising, control over the drug access process to the market.
- **Normative Pillar** – social obligation that arise from ethics, which are self-established.

Pharma companies are aware of the existence of these regulations and their impact on the variety of strategies that are legitimated to pursue. Their business strategies decisions must take into account what is formally allowed and what is not by the regulatory authorities such as the FDA in the USA or the EMA in EU. Pharmaceutical companies are heavily regulated to ensure they are in compliance. Even though government regulation lengthens the process of bringing new pharmaceuticals to the market, they ensure that the new drugs are rigorously tested for safety, efficacy and minimal side effects. At the same time also the mere marketing strategies must reflect what is ethically correct and what is not. Pharmaceutical marketing is in fact directed to the physicians and in recent years concerns over the influence of pharmaceutical detailing and industry gifts, which accounts for more than 80% of all promotional expenditures²⁵ have surged. Companies must ensure that their medicines are marketed in a manner that benefit patients and enhances the practise of medicine²⁶.

The regulatory environment is therefore significant enough to represent a barrier to entry. As a result M&A has become a common practise in the pharmaceutical industry. New companies and Big Pharma companies both benefit from mergers. The latter take advantage of opportunities to acquire profitable new products while the former benefit from the financial boost and expertise of a large partner.

²⁴ A set of organization that constitute a recognized area of institutional life.

²⁵ Gagnon M., Lexchin J. (2008). *The cost of pushing pills: A new estimate of pharmaceutical promotion expenditures in the United States*. PLoS Medicine.

²⁶ For more detail on pharmaceutical marketing see par. 1.4.1 Drug Life Cycle.

1.2.2 Porter's Five Forces Analysis

The structure pharmaceutical sector shows is singular: “It is characterized by a great variety of stakeholders, significant involvement of the State and a high degree of regulation aimed at achieving different objectives [...], ranging from supporting innovation to ensuring a high degree of public health keeping public expenditure under control.” (EU Commission, 2009, p. 19)

Micheal Porter created a “*Five Forces*” model aimed at determining the intensity of competition and subsequently the profitability and attractiveness of the industry to new players. This model provides an analytical view of the competitive forces that shape the market.

The *degree of rivalry* between existing competitors is moderate; the industry is fragmented despite big international players detaining a relatively consistent share of the total industry revenue with the top four companies detaining almost 37% of all revenue in the industry²⁷. The major players, the Big Pharma, can count of economies of scale in manufacture and R&D investments. The large investments together with the high level of fixed costs create pressure for all companies to fill capacity, thus strengthening competition in the market. In recent years the industry has witnessed more consolidation among players through M&A activity, which has eased rivalry allowing existing companies to diversify their portfolio and geographic grasp. The increase in competition, with existing firms controlling most of the capital and influencing the market, is also to be attributed generic manufacturing entering the industry's rivalry. This allows for more firms to capitalize on revenues and also motivate them to produce new-patented products. Nevertheless, especially in the biotechnology and ethical drug business segment, it is perceived a high degree specialization that implies a minimal product crossover and a reduction in direct competition.

Threat of new entrants, according to Porter (1985) refers to the degree to which new competitors can join an industry and actually represent a danger to the existing players. New entrants result in entrance only in profitable markets that yield high return, until the profit rate will fall towards a competitive level. In the pharmaceutical industry, nowadays, there are mainly established firms that have differentiated through the years one another by building a strong brand name reputation, which makes it makes it hard for new companies to compete against. More importantly however is the fact that new entrants are faced with high entry barriers, due to the large amounts of costs investments associated to R&D process. Even though the high degree of proprietary knowledge and patent protection allow firms to recoup from those expenditures by enjoying a period of market exclusivity. The nature of the market tends to be high-risk, time consuming and expensive; the profitability of companies in

²⁷ Turk S., *Brand Name Pharmaceutical Manufacturing in the US*, April 2015

this sector is dependant high skilled labour and innovation, as the key determinant of firms' success or failure. The stringent regulations regarding safety and efficacy together with the growing attention to costs puts companies under scrutiny on the cost-effectiveness of their products, requiring extensive clinical data. The start-up costs, the well-established competitive landscape as well as the strict regulatory environment pose a significant high barrier that will prevent new entrants with weak finances from entering the industry²⁸. If in the pharmaceutical sector threat of new entrants is relatively low, for biotech companies is even lower. Biotech, in fact, are "typically spin-off companies based on innovative products or processes resulting from discoveries in academic research" (MarketLine, 2012, p.16), which must bear long start-up periods with little profit and high fixed costs. They must therefore secure a high degree of venture capital backing, which may be difficult to obtain, given the long time period before any noticeable return on investment, and the relatively high risks of failure.

Threat of substitute in the industry is low. In the pharmaceuticals market the substitutes to branded drugs are generics. The threat of generics is substantial and is increasing as blockbuster drugs approach patent expiry. Generics can charge lower prices due to the fact that are exempt from costly clinical trial as they simply rely of the safety and efficacy data provided by the branded drug before them. Over-the-counter (OTCs) medicines are certainly more exposed to substitutes than prescription drugs (ethical drugs), as the former are directly purchased by the patient whereas the price of ethical drugs are heavily subsidized by either governments or health insurance and substitutes if exist may be more expensive.

The supplier and buyer power are assessed to be low to moderate. With respect to other sectors, indeed, the pharmaceutical industry is characterized by a peculiar supply and demand dynamics: on the one hand, from the supply side, innovative firms enjoy patent protection that grants them a monopoly which allows them to play in a reduced competition setting; on the other hand, from the demand side, the final consumers do not choose the product, clinicians choose for them and they do not sustain the economic cost of their purchase, since pharmaceuticals are reimbursed by the healthcare system. Buyers in this sector are in fact healthcare providers, doctors, managed care organizations (MCOs), government agencies and even drug retailers. Nevertheless medical practitioners hold much of the bargaining power because they wield significant influence in the prescription drugs business. Depending on the medical condition, there may be several different drug treatments available thus product differentiation weakens buyer power. Conversely, where generic equivalents to a branded drug exist, differentiation is increased and buyer power enhanced. However, buyer power is diminished until this patent protection expires and generic versions are marketed. Hence, in the face of generic drugs, buyers will show greater price sensitivity. Due to the primary need of the product and the fact that costs are almost entirely

²⁸ Grant, R.M., *Contemporary Strategy Analysis*, John Wiley & Sons, 7th edition, 2010.

borne by the government, demand is inelastic.

Suppliers are manufacturers of active pharmaceutical ingredients (API), which fall in a sub-sector of the chemical industry. To increase the degree of independence and thus reduce supplier power a lot of leading firms have backward integrated, investing in fine chemical manufacturing. On the contrary, small players with reduced chemical synthesis capability are still much reliant on APIs manufacturers. Switching costs from contracts' early exit represent one the suppliers' bargaining power driver, even though this is lessened by avoiding reliance on one particular company. In fact, laboratory equipment and chemicals show little differentiation, so that pharmaceutical companies can enjoy a high degree of choice in order to obtain the best cost-quality relationship, reducing supplier power.

Overall, the industry is high-risk, time consuming and expensive as the result of strict government regulations and the large capital investments required to reach economies of scale in manufacturing and to develop R&D pipelines.

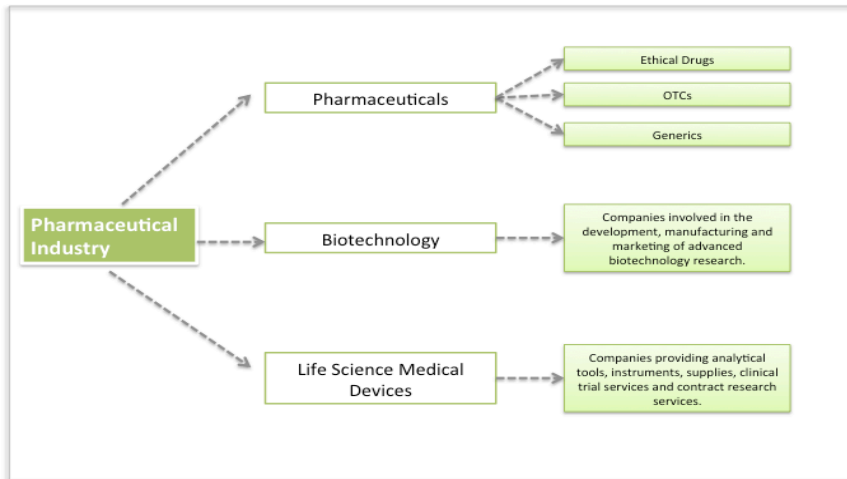
1.2.3 Industry Segmentation

As we have seen the industry is complex and extremely dynamic, nevertheless it may for simplicity be segmented in three main businesses²⁹: pharmaceuticals, biotechnology and life science medical devices (Figure 10). The pharmaceuticals business comprehends both the “ethical” drugs³⁰, the healthcare products in which the *Big Pharma* compete and the Over-the-Counter (OTCs). Both these products can be present in the market either in the form of branded drugs or of generics after patents' expiration. The biotechnology, instead comprehends all biotech products such as vaccines and biologics produced from living organisms, therefore more complex molecules, while the life science medical devices concerns all the analytical instruments and clinical tools used by both pharmaceutical and biotech companies.

²⁹ Zoli, Elisa, *Prede e predatori: il ruolo chiave dell'M&A nell'industria delle Big Pharma*. Tesi di Laurea in Finanza aziendale avanzato, LUISS Guido Carli, (A.A. 2009/2010).

³⁰ So-called “ethical” because by definition they are medicines which may be sold only under a written prescription from a medical practitioner.

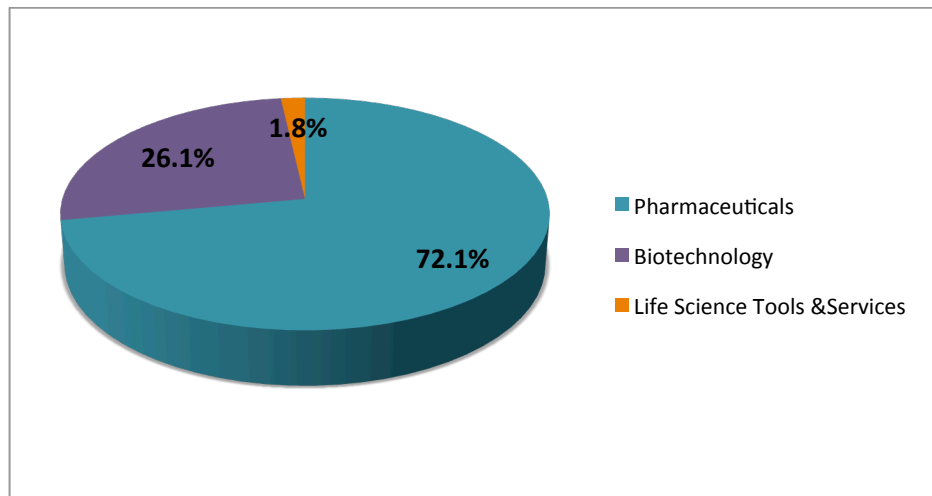
Figure 9 Segmentation of the Healthcare Industry



Source: As elaborated from E. Zoli, 2010.

The following graph (Figure 11) highlights the weight of each of these businesses on the industry total revenue; it shows also how the pharmaceuticals business alone comprises 72% of the industry value³¹.

Figure 10 Global Category Segmentation (% share)



Source: Elaborated from MarketLine, Sept. 2012.

Even though in everyday life we usually classify them all as medicines, it is important to distinguish among the variety of different healthcare products available on the market, which can be summarized in three main categories: *Originator drugs*, *Generics* and *Over-the-Counter (OTC drugs)*.

³¹ MarketLine, *MarketLine Industry Profile Global Pharmaceuticals, Biotechnology and Life Sciences*, September 2012.

Originator pharmaceuticals (or also Ethical Drugs) are medicines that can only be acquired with a prescription. They are developed through extensive R&D process followed by clinical trials. Because the R&D phase is associated with high capital investments and risks, the innovator relies on intellectual property rights (IPRs), such as patents, as well as reimbursement by payers to protect its product and justify the expenditure to bring it to the market. This type of drugs can either be chemically synthesised or developed through the use of biotechnology. These are usually defined biologics³² and “are typically proteins and antibodies derived from genetically modified living sources such as bacteria, yeast, or mammalian cell” (KPMG, 2015, p.2). While traditional pharmaceutical products are inorganic small-molecule compounds chemically synthesized, biologics derive from living organisms and are therefore larger and more complex molecules. Biologics have gained traction in the past several years, with more than \$150Bn dollars in global sales in 2013 and by 2020 they are predicted to produce \$290Bn in revenues and comprise 27% of the pharmaceutical market³³.

The global market for ethical drugs had total revenue of \$946.1Bn in 2016, with a compound annual growth rate (CAGR) of 6.1% between 2012 and 2016. Even though the global market slowed down in 2016, it is forecasted to speed up again in the coming years, with an anticipated CAGR of 6.5% between 2016-2021 driving the market to a value of \$1294.2Bn by 2021³⁴. By applying a geographic segmentation on last year total revenue, it emerges right away the leadership in terms of value generation detained by the US, with a share equal to 39,8%. The US continues to be a good market for constant growth and its sheer market size makes it attractive for doing business. Beside the US, Japan and China are the largest global pharmaceutical markets followed by the four biggest European markets³⁵. Emerging countries and in particular China are yielding the strongest growth every year compared to European states whose growth has smoothed due to the healthcare spending pressures.

As previously emphasized R&D activity is essential in preserving a strong market leadership because research aims at introducing in to the market not only new drugs but also “follow-on” medicines (also known as me too drugs), which are improvements on existing marketed medicines throughout new combinations, formulations or dosage reduction in order to obtain an extension of patent protection. The recent development and increasing competitive pressure from generics entry in the market are slowing down the earning dynamics and pharmaceutical companies’ profit margins. In this context the burden and the risk associated to such investments in R&D have amplified such that innovation have relatively weakened.

³² Sometimes are also referred to as biotechnology or large-molecule drugs.

³³ Deloitte, *Winning Biosimilars: Opportunities in Global Markets*, 2015.

³⁴ MarketLine, *MarketLine Industry Profile: Global Pharmaceuticals*, June 2017

³⁵ These are: France, Germany, UK and Italy.

Generics are basically identical copies of the originator chemically synthesized drugs, containing the same active pharmaceutical ingredients (APIs), duplicative in strength and dosage form, but sold at a lower price. When market exclusivity granted to branded drug expires “generic manufacturers are able to [...] bring to market generic versions of the original brand molecule which contain the same active substance, produce the same therapeutic effect and are manufactured to the same quality as the original product” (IMS Institute, 2014, p.6). Since generics are an exact copy, they don’t need to replicate clinical trials to obtain market approval, this allows non-branded generics companies to compete on prices, producing higher volumes by leveraging on an efficient chain of production and distribution chain³⁶.

They represent a separate world with respect to ethical drugs in terms of regulations, market dynamics and characteristics. Indeed, at the end of patent protection the drug becomes a commodity that can be easily replicated by many firms. The introduction of generics into the market has a double effect: a price effect – with price wars to face new competition – and market share effect – with branded products lose their leadership in the market. Overall the global generics market is characterized by a high degree of competition, where firms usually compete on prices in the absence of brand loyalty, that causes a critical consumer volume to be instable and too dynamic. Only in Europe the market grew by 5.5% in 2016, reaching \$49.5Bn in 2016 with a CAGR of 5.8% in the time period between 2012 and 2016³⁷. Demand is expected to rise, as payers are more than ever focused on costs reduction, and generics spending is expected to increase from 27% in 2012 to 36% by 2017³⁸.

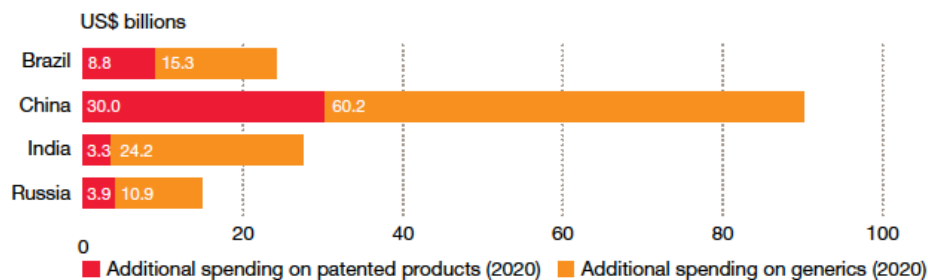
Generics have been present in the market since the ‘70s and if on the one hand they have benefited the society on the other hand they were responsible for a significant sales drop at the end of patent protection across all pharmaceutical firms. In fact, they shortened the recoup time firms had to recover their investments in R&D, increasing the pressure on prices and competition. The growth of generics is challenging branded companies, which face revenue and market share loss in both developed and emerging markets. Particularly in growth countries, which still lack financial power to reward innovation and for whom “near-term economic uncertainties are also likely to render progress in reforming their healthcare systems uneven [...] most of the projected increase in pharmaceutical sales over the next decade is expected to come from generics rather than patented products” (Figure 11)(Pwc, 2012 p.20,).

³⁶ 3-5 year development timeline and \$1-5M in development costs to produce a generic drug.

³⁷ MarketLine, *MarketLine Industry Profile: Generics in Europe*, January 2017.

³⁸ Deloitte, *2016 Global Life Sciences Outlook: Moving forward with cautious optimism*, 2015.

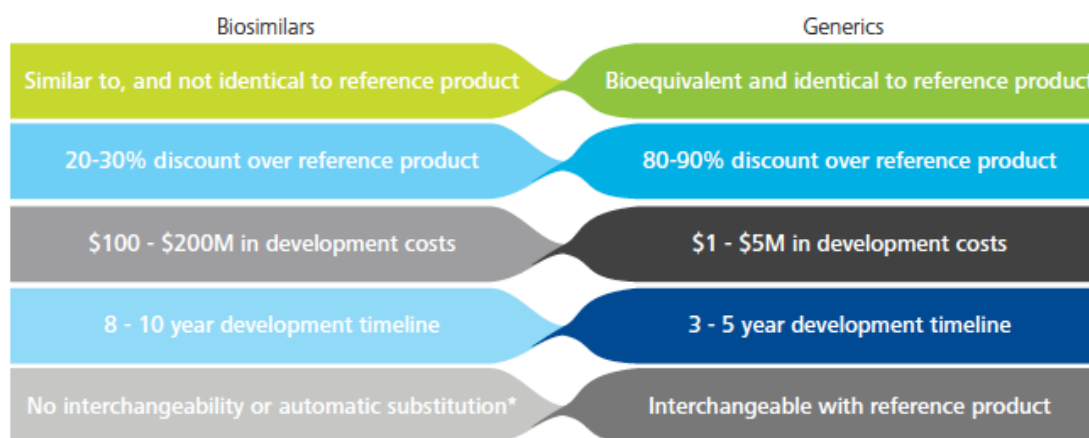
Figure 11 Patented Medicines vs. Generics Spending in Growth Markets³⁹



Source: Pwc, 2012.

Biosimilars or follow-on-biologics are nothing more than the generic version of a biologic drug. They are similar but not 100% identical to the innovator biologic drug they refer to. Since biologics are produced “via complex biological systems and production methods, biopharmaceuticals manufactured by companies other than the original drug innovator are not identical molecular copies. Thus the name biosimilars was created for products that are similar, but not identical, to reference biologic agents, [they] require extensive (and expensive) regulatory studies and assessment distinct from those required for generics” (KPMG, 2015, p.2). Therefore the development and implementation of guidelines by regulatory authorities to determine the extent of testing necessary to establish similarity has been a key challenge in recent years. As a matter of fact gaining market approval for biosimilars is far more complex than for generics and it involves costly clinical trials⁴⁰. The following graph highlights all the main differences between common generics and biosimilars (Figure 12).

Figure 12 Key Differences between Biosimilars and Generics



Source: Deloitte, 2015.

³⁹ All Sales are expressed in US dollars at constant exchange rate (CER).

⁴⁰ International Trade Administration, *Top Markets Report Pharmaceuticals*, 2016.

Since biologics are among the highest-cost treatments available on the market⁴¹ and the price offered by biosimilars are drastically cheaper than their patented counterparts, they represents a lower-cost alternative, which is not only attractive but also indispensable in economies where expensive treatments are not financially feasible. Today, 48% of sales come from 11 biologics that are facing loss of exclusivity over the next seven years. “This along with the increasing worldwide focus on improving health care access and the cost of care presents an attractive opportunity for biosimilars manufacturers” (Deloitte, 2015, p.1). Since the first approval in EU in 2006, there are there are more than 700 biosimilars approved globally⁴² and analysts have forecasted an uptake of \$25-35Bn by 2020⁴³.

Over-the-counter (OTCs) are medications that do not require prescription by the consumer in order to purchase them. They are considered safe to dispense for self-medication and as such can be sold in convenience store. OTCs cannot be considered as substitutes to ethical drugs, since the latter are prescribed for very severe pathologies. Nevertheless, “self-medication is increasingly seen as an alternative for many developed countries to reduce government spending on healthcare, with easily remediable conditions by drugs with little adverse side effects. These are available over the counter, and are a cheaper alternative to seeking a prescription from doctors. As such there has been a proliferation in recent years, making them accessible through different and new channels” (MarketLine, 2016, p.7).

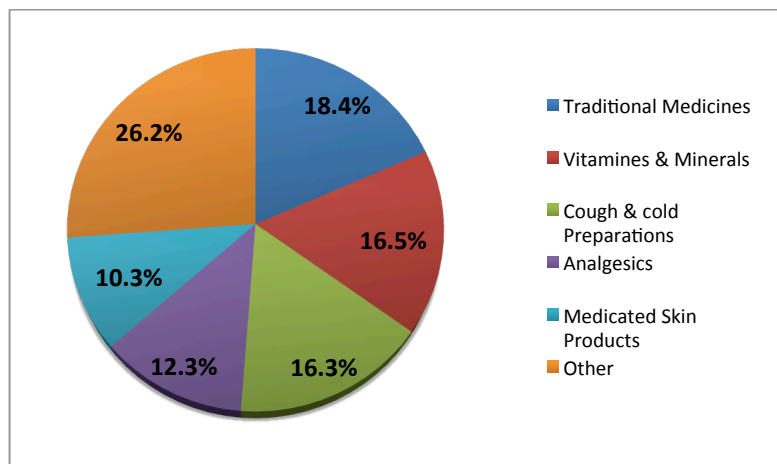
The global segment of the OTC pharmaceuticals generated in 2015 total revenues of \$0.13Bn, with a moderate CAGR of 3.6% between 2011 and 2015. With respect to the other segments, Asia-Pacific accounts for 35.3% of all the global OTC pharmaceuticals market value, followed by the US. The market is forecasted to remain stable with an anticipated compound growth for the period 2015-2020 of 3.6%, expected to drive the market to \$0.15Bn by the end of 2020. Traditional medicines account for the largest category within the OTC segment, accounting for 18.4% of the market total value, followed by vitamins & minerals and cough a& cold preparation both with a share around 16% (Figure 13).

⁴¹ KPMG, *How to compete and win in a world with biosimilars*, September 2015.

⁴² BioTrends Research Group, *Global Biosimilars Pathway and Clinical Development Activity: Where are the Biosimilars Hotspots?* 2014.

⁴³ Allied Market Research, *Global Biosimilars/ Follow-on-Biologics Market*, July 2014.

Figure 13 Global OTC Category Segmentation (% share), by value 2015.



Source: Elaborated from MarketLine, 2016.

The OTCs and the ethical drugs market follow different competitive rules: first and foremost OTCs can be purchased directly from the consumer without the doctor’s prescription. Moreover the latter are characterized by a higher customer loyalty to brands due to the cutting advertisement campaigns. Despite the R&D costs to bring new drugs on the market and the level of expertise required, which favour the big players, in the market it is observable the prevalence of many small and medium enterprises (SMEs). These are able to reach efficiency in terms of economies of scale and scope through strategic collaborations with big multinationals, which provides a win-win situation for both sides. Big multinationals offer financial support in exchange for constant innovation from new players.

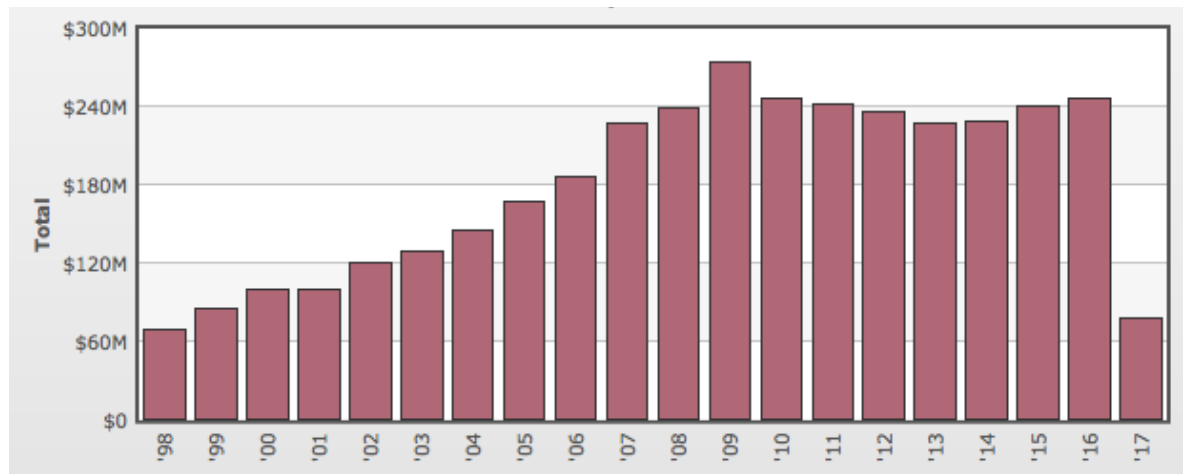
1.3 The Pharma & Biotech Business

Besides different healthcare products being present on the market, there are also diverse types of firms; it is important to understand their role in the market and how they connect in order to grasp the dynamics in the sector.

First and foremost we have the big multinationals companies, so-called **Big Pharma** that as the name may suggest are the ones to detain the greatest market shares, especially in developed countries. They are usually vertically integrated across all activities of the value chain and are able to concentrate the greatest amount of resources in the R&D process on drugs with a wide eligible pool in order to obtain an increasing number of APIs filings. These firms can leverage their size and international presence for lobbying activities to further increase

their market penetration (Figure 14) as well as to maintain their dominant position even after patent expiry. In the US lobbying is an activity widely diffused among pharmaceutical companies to influence political decisions and assure the *status quo* in terms of regulations and prices. According to the Center for Public Integrity pharmaceutical industry has invested from 1998 to 2006 \$855 Million in lobbying activities⁴⁴.

Figure 14 Annual Lobbying on Pharmaceutical and Healthcare Products



Source: Opensecret.org.

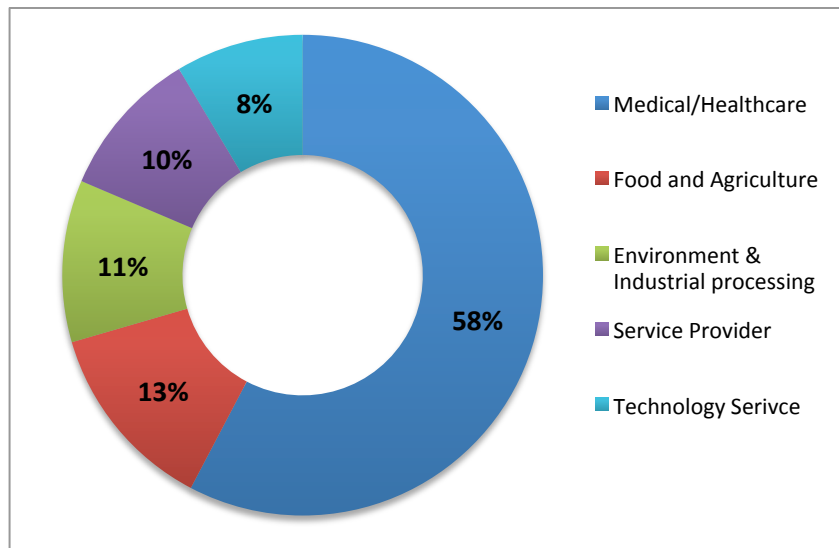
During the '80s the market witnessed the entrance of new players on the market: the **Biotech firms**, whose name literally means “technology applied to biology”. These were financially supported by venture capitalists and their main focus was, and still is, developing processes and products deploying numerous opportunities deriving from molecular biology and genetic engineering. The biotechnology market “consists of the development, manufacturing and marketing of products based on advanced biotechnology research” (MarketLine, 2016, p.7), for this reason the industrial sector in which can be applied are not only limited to the healthcare sector. Nevertheless the complexity of their output with respect to the most traditional pharmaceuticals induced a productive capacity shortage that drastically surged prices and limited biotech application to reduced volumes in niche markets. Many biotech firms planned a vertical integration along all the value chain but only few succeeded, among these Amgen represent a successful story. Other biotech companies nowadays left a stand-alone strategy to collaborate with the *Big Pharma* through strategic partnerships and licensing in order to earn a greater return on investment on R&D activities.

The global biotechnology industry was expected to generate \$358.9Bn in total revenue only in 2016, with a growth of 5.8% respect to the previous year. Even though growth slowed down in 2016 the market has been

⁴⁴ Tugaraza T. & Poole R., *Influence of drug company authorship and sponsorship on drug trials outcomes*, British Journal of Psychiatry, Vol.191, pp.82-83, 2007.

growing at a strong rate in the past few years – CAGR of 8.8% between 2012 and 2016 – and it is predicted to settle at a compound annual growth rate of 8% during the next five years. In 2021 the market is forecasted to reach a value of \$528.4Bn, which implies an increase of 47.2% respect to the 2016 market value⁴⁵. The US alone accounts for 45.9% of industry value in 2016, while Europe settle at lower than one fifth. The Medical/Healthcare segment, which includes biologics medicines, represents the most lucrative business in the global market with an incidence of 57.7% of the market in 2016 equal to \$207Bn (Figure 15).

Figure 15 Market Segmentation of the Global Biotechnology Market in 2016



Source: MarketLine, 2016.

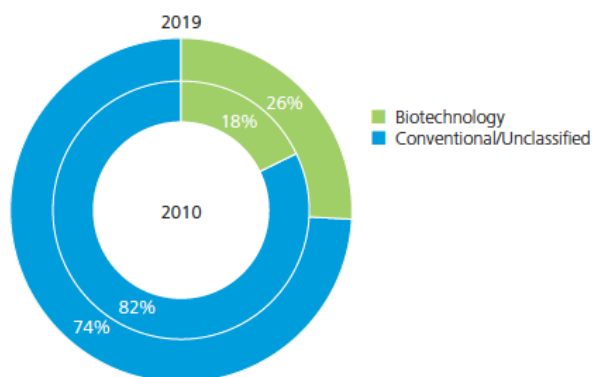
Innovation in the pharmaceutical sector has witnessed a growing importance of biotechnology. Biotech processes are widely diffused in development and test phases for new pharmaceuticals, but innovation from biotechnology in some therapeutic areas has not only been in terms of processes but also of curative products.

Indeed, in the life science sector biotech drugs continue to have traction and “Of the top 10 pharma products by sales in 2014, the majority of them were biotech drugs, [...] treatments for rheumatoid arthritis, Hepatitis C, and cancer figure most prominently in the list of the most sales-generating drugs” (Deloitte, 2016, p.3). Furthermore, with the increasing focus on specialty drugs and on personalized medicines, biotech companies are witnessing a significant growth in investment activity to develop new biotech blockbusters, considered a central driver for industry sales. Although the traditional chemical-based compounds continue to dominate the sector sales, biotech drugs have carved a niche for themselves such that biotech share of worldwide prescription drugs and

⁴⁵ MarketLine Industry Profile, *Global Biotechnology*, November 2016.

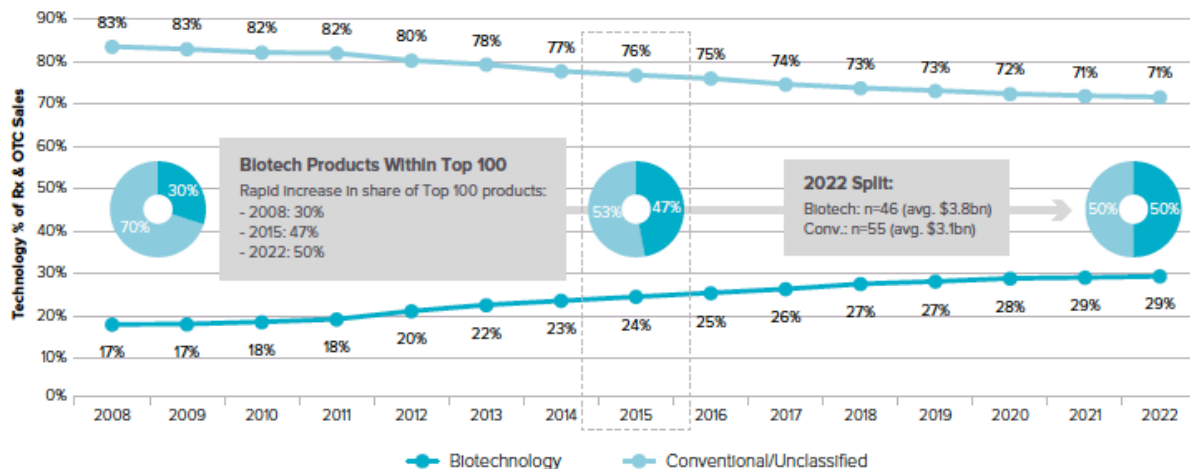
OTC pharmaceuticals is projected to reach 26% in 2019⁴⁶ (Figure 16). The uptake of biologics is forecasted to continue as new blockbuster will entering the market and according to EvaluatePharma (2016) in 2022 50% of the value of the top 100 products will come from biologics, since established chemical drugs will drop off patent cliff (Figure 17)

Figure 16 Global Pharmaceutical⁴⁷ Sales by Technology



Source: Deloitte, 2015; World Preview, 2015; EvaluatePharma, 2015.

Figure 17 Worldwide Prescription Drugs and OTCs Sales by Technology



Source: EvaluatePharma, 2016.

In the worldwide competitive scenario, but in particular in countries such the United States where the market is more developed, a high number of biotech giants together with biotech start-ups and SMEs compete fiercely in the business. To lower competition firms can differentiate their products in four main categories: vaccines,

⁴⁶ Deloitte, 2016 Global Life Science Outlook, 2015.

⁴⁷ Prescription drug and OTC pharmaceuticals.

monoclonal antibodies, insulin and TNF inhibitors. In this global outlook the undisputed market leader is Roche, which it is expected to further consolidate its position with the launch of novel biologic therapies in the coming years. Amgen is set to fall down the rankings due to patent expiration of many of its biologics (Figure 18).

Figure 18 Top 10 Companies for Worldwide Prescription Drug Sales from Biotechnology in 2022

Rank	Company	WW Sales (\$bn)			WW Market Share	
		2015	2022	% CAGR 15-22	2015	2022
1.	Roche	31.1	43.6	+5%	16.9%	12.9%
2.	Sanofi	14.9	25.3	+8%	8.1%	7.5%
3.	Novo Nordisk	15.1	24.4	+7%	8.2%	7.2%
4.	Amgen	18.8	23.2	+3%	10.2%	6.9%
5.	Bristol-Myers Squibb	4.5	18.2	+22%	2.5%	5.4%
6.	Johnson & Johnson	10.9	17.7	+7%	5.9%	5.2%
7.	AbbVie	14.8	15.5	+1%	8.0%	4.6%
8.	Eli Lilly	6.6	15.4	+13%	3.6%	4.6%
9.	Pfizer	11.9	14.8	+3%	6.5%	4.4%
10.	Merck & Co	7.9	13.0	+7%	4.3%	3.9%

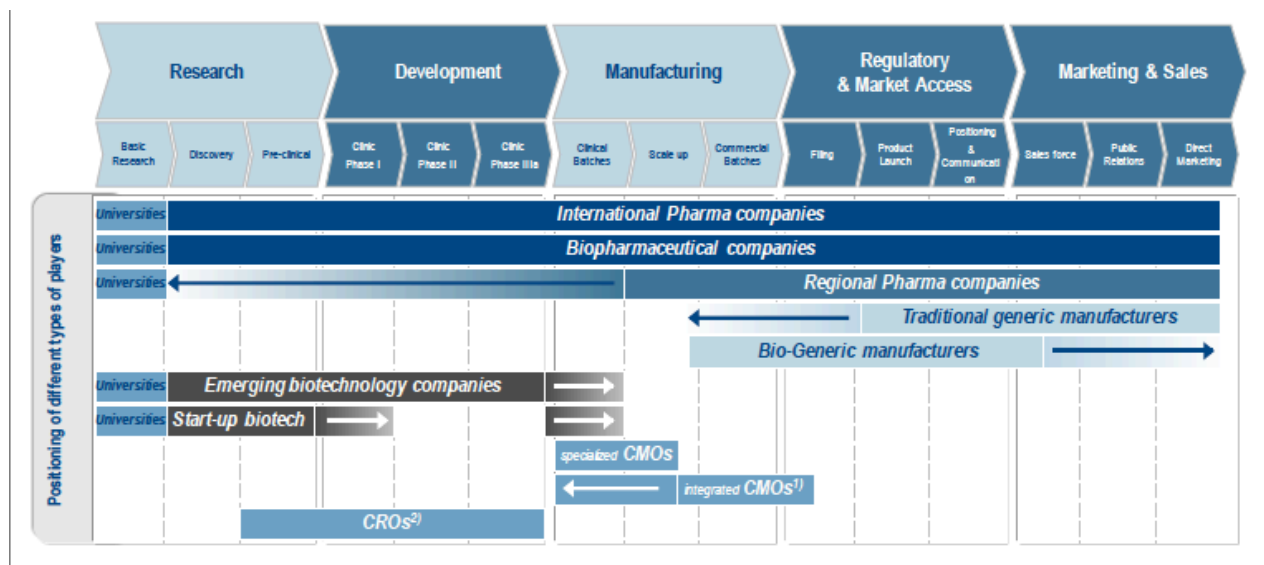
Source: EvaluatePharma, 2016.

1.4 The Pharma Value Chain:

Generally the phases of research and development (R&D), manufacturing, marketing & sales characterize every drug life cycle. All these activities are strictly interconnected and represent an integrated circuit that is necessary to reach the final endpoint: transform the initial investment in a new medicine viable for patients with medical unmet needs. The key strategic capacities are undoubtedly R&D and marketing, while the manufacturing activity, following the significant pressure on margins, has been subject to an improvement in productive efficiency through the rationalization of the number of productive sites and the relocation in geographic area with fiscal advantages.

The drug life cycle coincides with the value chain in the pharmaceutical industry and it is increasingly modular, with the Big Pharma being fully integrated companies along all the value chain while specialized players capturing only some of the value by positioning in specific phases (Figure 19).

Figure 19 The Industry Value Chain



Source: Arthur D. Little, 2016.

The highly competitive nature of the industry has resulted in biopharmaceutical companies to find new ways to minimize costs and maximize profits. The pharmaceutical industry has learned to economize on functions that were previously performed in-house and now are transferred to external providers. “Many large pharmaceutical companies have divested significant manufacturing and logistics facilities. They do this as they strive to realign strategic priorities, such as to accommodate drugs losing patents or a re-prioritization of where they wish to add

value (e.g. exiting a particular therapeutic area). The contract manufacturers have adapted and made use of (these) opportunities provided to them by both small biotech and large pharmaceutical companies” (Rh, 2017, p.5). Cost-efficiencies and rapid time-to-market are crucial factors in the pharmaceutical industry; by outsourcing get access to expertise and know-hows not available in-house at lower costs, spreading the risk of development and have to possibility to focus on their core business.

The market for Contract Research Organizations (CROs) and Contract Manufacturing Organizations (CMOs), which offer outsourcing services, is increasing and outsourcing – whether it’s in research, development or manufacturing – has become a common practise to both big and small pharmaceutical companies. While CMOs activities range from providing bulk chemicals to specialising in one particular aspect of pharmaceutical manufacturing, CROs range from large full service organization to smaller niche companies and play an important role in R&D. In fact, “when they first appeared focus was on drug discovery and preclinical work which has now shifted to include services such as clinical trials, drug manufacturing and also marketing. [...] They are full service collaborators (that) often become a permanent supplier of certain functions” (Swarting & Appelgren, 2011, p.21).

1.4 .1 Drug Life Cycle

The R&D phase is the core business of every pharmaceutical company and it is the phase when innovation takes place that culminates with an “idea” on which explorative research is conducted aimed at identify a target. In case of positive results the potential molecule is selected and therapeutic research begins, aimed at proving the value of the new drug. At the end of the basic research that demonstrates efficacy, it starts the pre-clinical trials, which instead determine the dosage and safety profile. If the results obtained so far are affirmative they will support the clinical development in which the drug will be tested on humans. The R&D phase ends with a dossier, including all scientific data, to be filed to the regulatory authorities in order to obtain the permit to access the market. After obtaining regulatory approval, production can begin which must adhere to the specific safety measures in a given country.

As a last step in the value chain there is the activity of marketing and sales, which in recent years is significantly growing as source of competitive advantage. The pharmaceutical marketing has different operating modes according to the type of medicine that must be marketed, to the stakeholder that influence the acquisition process, the distribution network and nonetheless the country in which the firm operates. The most traditional

marketing forms consist of specialized and competent sales force⁴⁸, which by representing the firm interact directly with the prescribing clinicians. Therefore approval from physicians, the major player in prescribing ethical drugs, is pivotal to influence sales volumes. On the contrary, marketing activities for OTC drugs is directed to the final consumer and it is considered the cardinal point in the selection and subsequent buying process. For this reason advertisement is the mainly used for OTC in order to increment brand awareness to the final consumer and competitive advantage over competitors.

Marketing activity has a double purpose: spread information and differentiate them from competitors, especially when in the same therapeutic area there are similar products, in order to improve the overall company market share. In order to avoid inappropriate prescriptions pharmaceutical marketing activities undergo rigid regulatory compliance, in particular when promotional activities are focused to clinicians or directly to the patient.

In the pharmaceutical market customer loyalty is a key selling determinant when a product has the first mover advantage that can only be overcome if subsequent launches offer superior clinical benefits and relative low switching costs. In the ethical drug business, marketing activity frequently takes the form of scientific information as the most effective mean of promotion. Another promotional channel in great expansion are publication specialized scientific magazines, which reach directly subscribed clinicians at lower costs. The Direct-to-Consumer Advertising (DTCA), both through the television and the Internet, is also gaining consensus. It is evident though, how this particular way of promoting pharmaceutical products is altering the traditional schemes requiring a change in the marketing mix, in the way resources are allocated and in the doctor-patient-pharmaceutical company relationship. Nowadays the DTCA is not allowed in Europe⁴⁹, with the exception of vaccines, while is widely diffused in the USA and it's gaining a high Return on Investment. IMS Health Inc. has demonstrated how a \$1 incremental spending in DTCA returns from 2 to 10 dollar of sales.

1.4.1.1 The Price Build-up

Ensuring that patients receive the correct medicine at the appropriate time and from a convenient location requires a complex value chain that involves three major components: manufacturing⁵⁰ of the medicine, distribution⁵¹ to the dispensing point and dispensing to the final user. Each step contributes to the price build-up

⁴⁸ In Italy the so called "*Informatori Scientifici del Farmaco*" (ISFs)

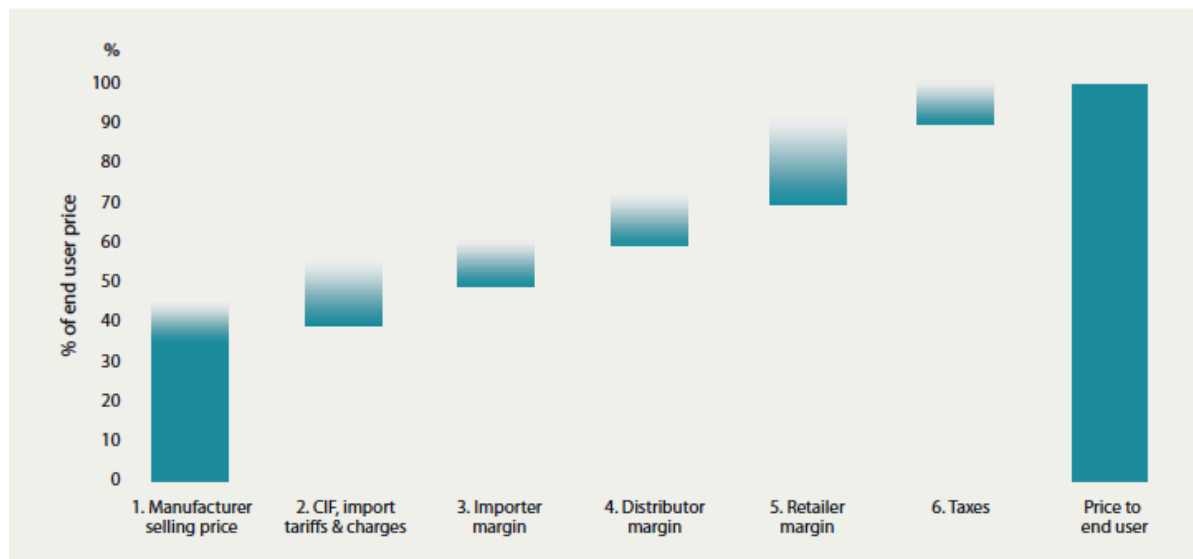
⁴⁹ *Dir. 92/98 cap.2, art.3*

⁵⁰ IMS defines manufacturing of the medicine as "the number of steps involved from the initial research and development phase to gaining regulatory approval which allows a medicine to be sold in a market to the final commercialization phase".

⁵¹ The distribution process of pharmaceutical products is not uniform across all nations; on the contrary it has particular characteristics from country to country. Below are summarized features common worldwide.

of the medicine and the World Health Organization (WHO) together with the Health Action International (HAI) assess that there are six key components to affect the price levels and subsequently the margins from the manufacturing ex-factory price to the price paid by the end user (Figure 8).

Figure 20 Price Build-up Illustration according to WHO/ HAI



Source: IMS, 2014.

Following the IMS analysis (2014) on the relative magnitude of each of these six price components is instructive in understanding what are the costs incurred by each stakeholder along the value chain as well as the value added that they contribute and therefore what are the determinants of their profit margins (Figure 21).

- Manufacturers:** the greatest expense they incur into is R&D, however it's difficult to put an exact figure on the cost of bringing a new medicine into the market, as this depends on the type of drug, the level of innovation and the magnitude of risk involved. On the contrary generics manufacturers have low development and manufacturing costs, their principal mean of promotion are trade incentives and large discounts in order to secure large sales volumes. Once a medicine reaches the market other costs to take into account are that of promoting the product and educating the key stakeholders to its benefits. Although generating a new drug directly benefits patients in need, the value added however it's not only the medicine per se; on top there is the scientific knowledge and technological advancement that can diffuse to other sectors of the economy as well as the educational efforts that can help those working directly with patients to ensure they receive the highest standard of care. Value added by generics manufacturer is competition, which can help payers achieve costs savings on older treatments while investing in new ones. Unlike prices for any other products, medicines prices are set by unique country

pricing policies. However is worldwide recognized that the negotiated price rarely coincides with what the manufacturer receives; among the factors that impact the level of manufacturers' net price trade discounts are the largest. These discounts are offered by manufacturers to wholesalers or pharmacies and vary in size depending on the purchasing power of the buyer and the level of competition.

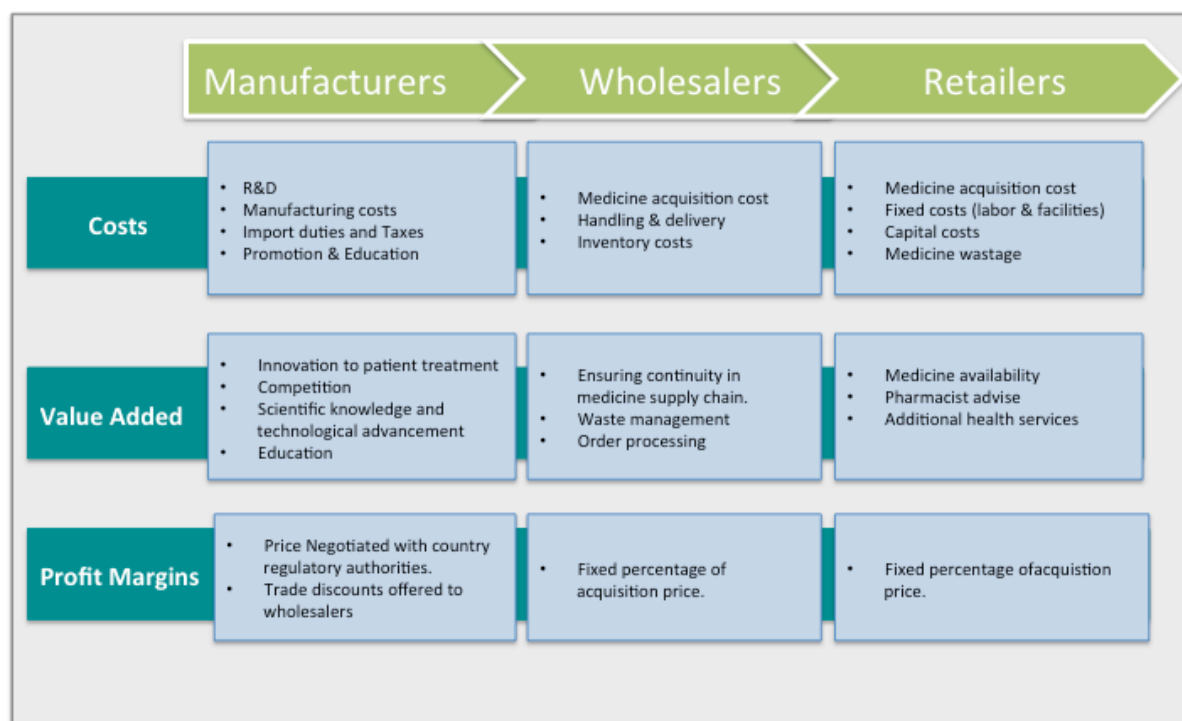
- **Wholesalers:** the distribution to the dispensing point includes the transportation and handling of the medicine from the manufacturer to the end user, whether it is a retail pharmacy hospital or dispensing doctor, and it is carried out by importers and wholesalers⁵² that ensure the continuous supply of medicines. Pharmaceutical distribution needs to meet the logistical challenge of serving a large number of pharmacies with products sourced from manufacturers, often in a short period of time. They need to invest in inventory and the cost of carrying inventory includes warehousing cost, capital stock and obsolescence. Their key functions are to meet the unpredictable patient needs, by supplying medicines from manufacturers, without requiring the retailer to hold large inventories on-site, to provide the necessary working capital for pharmacies to allow them to purchase the required drugs, before receiving end user payment, finally, in some markets wholesalers also provide a broad set of commercial support to independent pharmacies to improve the operation of the business. Their margins are usually regulated as a fixed percentage of the price.
- **Retailers:** Retail pharmacies have an important role in terms of logistics to play: they dispense the right drug at the right time with the correct dosage. Their task, however, entails also correcting prescribing errors, processing prescriptions as well as advising and education the patients any possible adverse events. In recent years the pharmacist has dedicate more time in mitigating the impact of medicines shortage by sourcing drugs and finding alternatives. Nowadays also the retailer business model is undergoing changes and the pharmacist no longer simply provides medicines, but it offers additional services that help maintain patient health such as training on administration of medications, blood pressure testing and education on disease management. Besides the fixed costs, retailers are subject to variable costs such product acquisition costs and capital cost of inventory. Their remuneration is determined by two main factors: the level of discounts negotiated from the wholesalers, which determines the acquisition cost of the medicine and the mark-up, usually a fixed percentage, paid by the end user.
- **Government taxes** are shown to be a leading component in the price build-up of medicines. Import duties and value added taxes (VAT) are the most common forms of taxes used but there are also other

⁵² For those medicines that are imported, there is often an additional step from the importer who organizes the logistics of bringing the medicine into the country, which are then transferred to the wholesaler for domestic distribution. In some cases the two entities are vertically integrated, decreasing the number of steps in the distribution stage of the value chain.

country specific taxes that can be applied.

“The combination of the value added at each step as well as the costs incurred provides the basis for understanding the pharmaceutical value chain [...], however the degree to which these occur in specific markets will differ depending on the sophistication and efficiency of the supply chain and common commercial practices” (IMS, 2014, p.2).

Figure 21 Breakdown of Medicine Value Chain



Source: Elaborated from IMS, 2014.

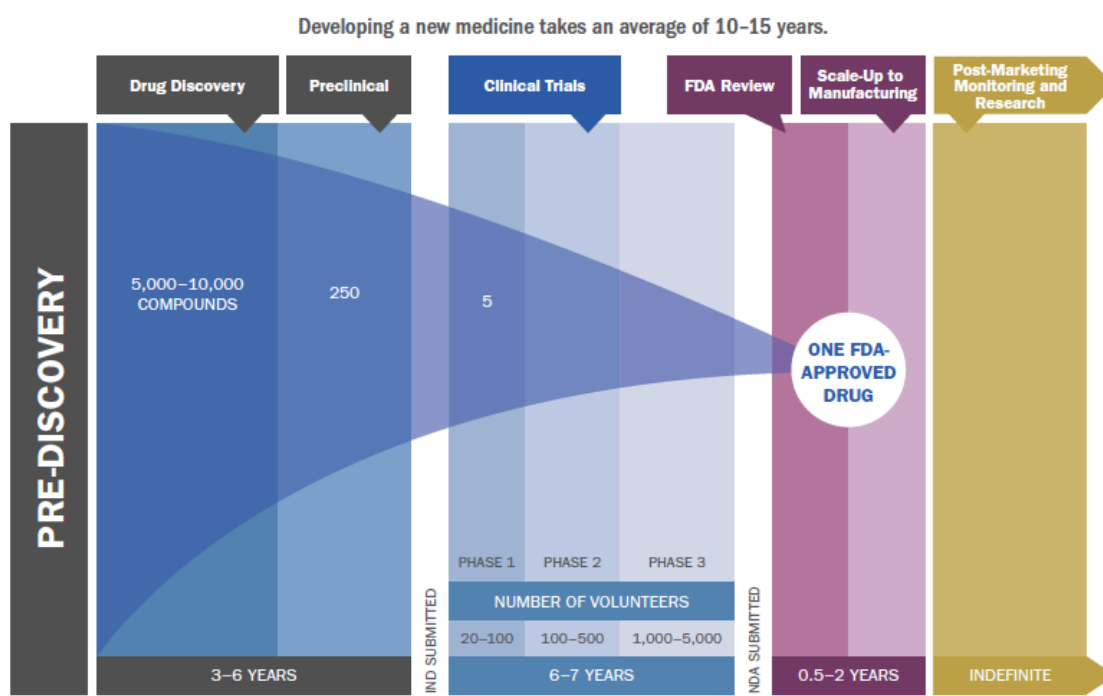
1.4.1.2 R&D: The Core of the Industry

A new drug that enters the market must be a tool in terms of efficacy, safety and usage. Research and development is a process exposed to high risks of failure, extremely lengthy and costly. The steps – which thoroughly assess safety and efficacy – that bring a molecule to be approved and be available on the market, take about 10 to 15 years. At best one molecule out of 10.000 compounds synthesized will succeed at arriving at the pre-clinical studies and only one out of 10 will successfully overcome every phase of the development and delivered to the patients (Figure 22).

The R&D process starts with a drug **discovery phase**, whose first step involves basic research studies to understand a disease as thoroughly as possible. Once scientists have a sufficient understanding they select a target for a potential medicine – usually a molecule that plays an important role in the disease. Further studies are performed to determine whether a drug can act upon that target.

The initial research activity starts from the identification of a therapeutic need. When one or more compounds, called lead compound, demonstrate relevant biologic activity on the specific target considered, a series of tests start to evaluate potential toxicity and determine the chemo-physic properties. Therefore only the molecules with the best profile are selected.

Figure 22 R&D Process



Source: PhRMA, 2012.

In a first phase of research the interaction between the potential drug and the targeted biomarker is studied in order to design the best structure for the molecule that most interact with the biomarker under analysis. In this way a predetermined molecular structure is decided, with a high potential of success from the biologic activity point of view, and used in the phase of chemical synthesis. Afterwards, in a second phase thousands of compounds are verified for the biomarker target through an approach based on combinatorial chemistry. Both these phases of basic research last 2-3 years and represent approximately 10% of the total investment. The objectives of this base research are the isolation, the synthesis and the design of a potential active ingredients that have a key role in the resolution of certain pathology; a lead compound is therefore identified to undergo

subsequent research: pre-clinical development, whose primary endpoint is to verify in laboratories all possible characteristics, both positive and negative, of the drug. Since the early stage of discovery, researchers think about the final product in terms of formulation and delivery mechanism.

Only few hundreds compounds move on to **pre-clinical testing** usually last from 2 to 3 years and requires almost 30% of the total investment. Laboratory studies and animal tests are conducted to determine which candidate compounds are suitable to be tested in humans. At the end of this phase researchers have one to five compounds deemed to be safe and suitable for testing in humans. Therefore companies submit to the FDA or EMA an Investigational New Drug Application to seek approval for clinical trials.

Clinical development is articulated in three phases – Phase I, Phase II and Phase III – and aims at evaluating the therapeutic properties of the drug, test the efficacy and safety profile on humans and if clinical benefit is proved prepare for the regulatory approval. Clinical trials typically last from six to seven years, involving thousands volunteers. Phase I trials test the drug on a small group of healthy volunteers with the sole purpose to test the safety of the compound. Phase II, instead, involves a larger group of patients and it aims at determining the effectiveness of the medicine, optimal dosage and schedule while examining short-term side effects. Phase III trials test the drug on thousands people to generate statistical significance about safety, efficacy and benefit-cost ratio. Once clinical testing are completed and the results are positive, then the firm can actually submit New Drug Application (NDA) or Biologics Licence Application (BLA) to the FDA in order obtain regulatory approval to market the drug.

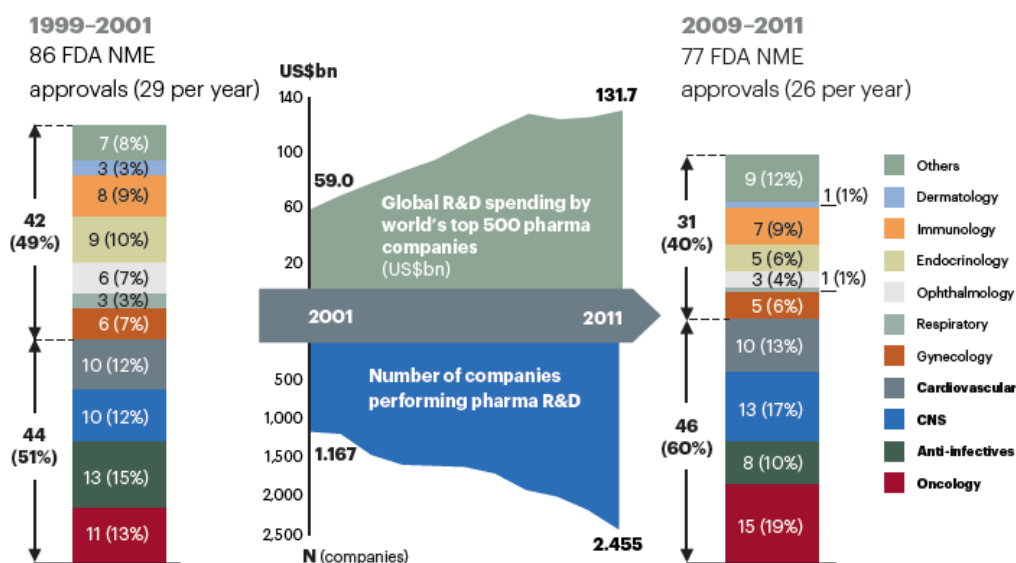
Even after a drug has accessed the market, companies or the regulatory authorities may continue to run clinical trials, so called phase IV studies, to monitor how a medicine it is being used by care providers and patients as well as to confirm its safety, efficacy profile and long term side-effects. Conducting continue research on approved medicines allows firms to better understand potential use in other indications and study possible combination with other medicines important to medical progress. Thanks to these observational studies there is a constant update on the risk-benefit profile of the medicine. In this context the role of the pharmacovigilance is crucial in collect information and registry all possible adverse events deriving from the medicine.

1.4.1.2.1 R&D: the Productivity Crisis

Since few years ago, despite the continue increase in R&D spending drugs approval were lagging. In fact even though spending during the period 1992-2008 more than doubled, the new molecule approvals have

dropped⁵³. In fact, if in the period between 2002 and 2004 \$78Bn were spent annually on drug R&D and 32 filings for approval were received, between 2009 through 2011 R&D spending increased to \$128Bn with only 29 new filings (Figure 23). A large number of compounds were indeed generated by biotech ventures that backed up the pharma companies with efficient R&D. Between 2002 and 2011 both pharma and biotech sectors spent almost \$1.1 Trillion on R&D but with scarce results since the annual output actually flat-lined in the past decade. “In the 10 years to 2011, the FDA approved 308 new molecular entities (NMEs) and biologics. Given how much the industry invested in R&D each year during the same period, that means the annual average cost per approved molecule ranged from \$2.3 billion to \$4.9 billion” (Pwc, 2012, p.24).

Figure 23 R&D Activity compared to NMEs Approvals



Source: ATKerney, 2013.

In the capital markets in 2001 market capitalization of big pharma per R&D dollar spent was \$42, in 2011 it was almost halved to \$20. As a result R&D budgets were subject of cost-cutting initiatives in terms of coast-saving and efficiency improvements. In the last release of *Pharma2020* by Pwc, it is claimed that because of the surge in R&D costs companies will be either acquired and stripped of their assets – indeed reducing R&D costs has become the main rationale for many M&A deal in the industry⁵⁴– or they will separate R&D from their revenue generating activities to reduce risk and unlock shareholder value. As a matter of fact, due to the massive costs as well as the increase complexity and fragmentation of the require know-hows associated to R&D process, it is expected that sooner 70-80% of research and development, nowadays performed in-house, will be outsourced to

⁵³ Arthur D. Little, *Trends in the Pharmaceutical Industry*, January 2016.

⁵⁴ ATKearney, *Unleashing Pharma from the R&D Value Chain*, 2013.

third parties. Indeed, firms in the industry are all already trying to do ‘more with less’ – as already observed in the changes observed in the value chain – but there’s no sign of a big surge in productivity. An argument proposed to account for pharma’s poor performance in R&D is that the industry’s now focusing on fewer therapeutic areas with more complex diseases. Furthermore the approach adopted by companies in the last years over the past 20 years “has often yielded compounds only marginally better than existing therapies, yet require(ing) larger, longer, and more complex trials. To fund them, companies have shifted resources away from drug discovery to late clinical development; this has hurt innovation and amplified the crisis brought by the expiration of patents on many best-selling drugs” (Munos & Chin, 2011, p.1).

Whatever diseases a company decides to focus on and whatever methods it chooses to discover and develop new treatments, it is imperative to keep an open mind until clinical proof of concept; “*the great tragedy of science – the slaying of a beautiful hypothesis by an ugly fact*”⁵⁵. It’s even more painful when that hypothesis has consumed a lot of money⁵⁶.

1.4.2 Reshaping the Value Chain: New Business Model

“Significant opportunities exist in the global marketplace but challenges exist, as well. Spending growth in pharmaceuticals, biotechnology and medical technologies is projected to follow an upward trend due to increasing demand, but pricing challenges are still an issue. Industry margins are being eroded by high discounts, retail sector price controls, public sector purchasing policies, and the move to value-based care. Strong economic growth looks hard to come by in many countries; therefore, assumptions on health spending may need to be revised downward. In response to today’s dynamically changing clinical, regulatory, and business landscape, pharma, biotech, and medtech companies are re-evaluating and adapting traditional research and development (R&D), pricing, supply chain, and commercial models.” (Deloitte, 2016, p.2)

Indeed, pharmaceutical companies’ business model has altered with respect to the previous decades; “in the 1980s and 1990s, (firms) made medicines for chronic diseases, marketed them to doctors and focused on turning them into blockbusters. These days, (they are) concentrating on specialist medicines, which it markets to healthcare payers – who use different, and more rigorous, selection criteria” (PwC, 2012, p.38). Scientific advancements have made drugs ever more targeted and together with diagnostics technology, those few

⁵⁵ Thomas Huxley

⁵⁶ PwC, *From Vision to Decision: Pharma 2020*, 2012.

individuals that will benefit most from a given therapy can now be selected from large populations. “This means that after many decades of running a successful “blockbuster” model for new drugs, the business model for companies has evolved towards specialty pharma, targeting diseases with a low incidence and a more limited number of patients with a high medical need”. (Arthur D. Little, 2017, p.15) In parallel, technology advancements are about to have a revolutionary impact on pharmaceutical business models, like it has previously occurred in many other industries, which will likely cause a significant disruption to established value chains, with competition coming from outside the traditional healthcare sector – tech companies longing to reap large profits from e-health concepts.

Digital health will revolutionize pharmaceutical industry’s current business model; a study performed by Arthur D. Little⁵⁷ indicated that managers expect digital health to significantly extend current business models, or even to create completely new ones for their industry. Companies such as Merck and AbbVie are already offering digital services to support patient compliance, adherence and collaboration and more innovation is coming to the healthcare sector. “The proven, classical, product-centric approach [...] (will need) to embrace the required speed, new collaboration needs, flexibility and ability to learn quickly in order to become patient-centric, integrated and multichannel” (Arthur D. Little, 2017, p.33).

1.4.2.1 The impact of Intellectual Property Rights (IPRs) on value creation

As previously said the value creation process determines the drugs’ life cycle and key parameters to be optimized (Figure 23). Pharmaceutical companies over the years have managed to optimize the life cycle by reducing the time to market and the time to reach maximum profit, while increasing the peak sales before generic entry⁵⁸.

The traditional value creation system, as in every other innovative industry, is based on intellectual property rights (IPRs) and supported by patents. IPRs play an extremely important role in the pharmaceutical industry to incentivize the extensive efforts in R&D and for the protection of newly generated knowledge.

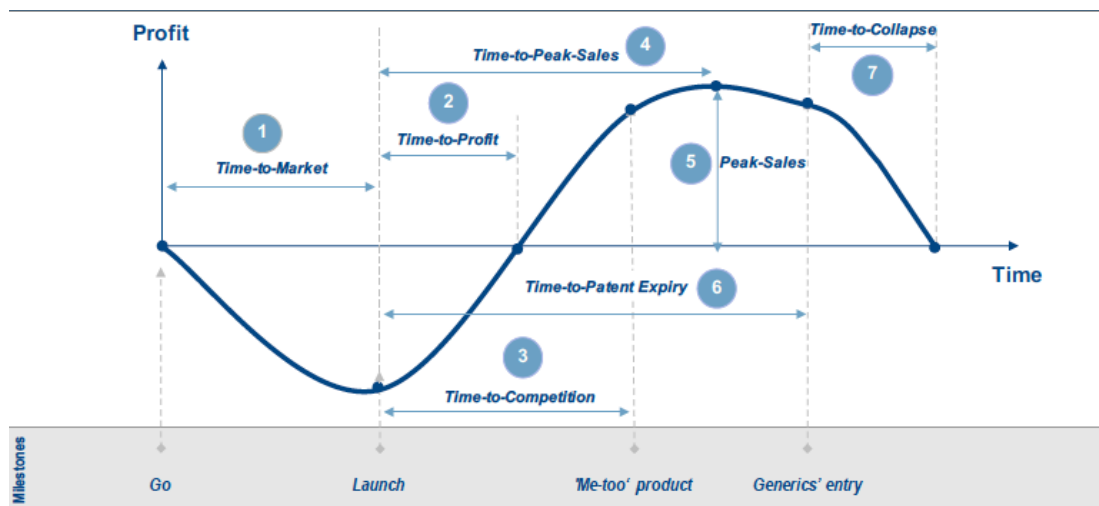
Scientific knowledge, especially after it has been published and spread to the community, assumes the typical characteristics of a public good – hardly excludable and non-rival – it thus become accessible to everyone. For

⁵⁷ Arthur D. Little, *Impact of Digital Health on the Pharmaceutical Industry: Will Business Models be Reshaped by Digital Health?*, 2014.

⁵⁸ See par. 1.4 Value Chain on CMOs and CROs and how they have helped companies to become more efficient.

those reasons, “pure competitive markets are unable to generate a stream of quasi-rents sufficient to motivate profit-seeking firms to invest resources in [scientific knowledge] production” (Dosi et al., 2007, p.471).

Figure 24 Major Influence Points in the Drug Life Cycle



Source: Arthur D. Little, 2016.

Intellectual property rights (IPRs) have been developed as incentives for technological innovation and are theoretically rooted in a framework of “market failures” in knowledge generation. By providing IPRs, “the government assures the inventor the right to exclude others from using the outcomes of his creative activities without his authorization. Thus [...] (giving) the inventor a legal monopoly to exploit (the) invention and captur(ing) the economic benefits for a limited period of time” (Archibugi et al., 2010, p.138). Nevertheless, as opposed to this mainstream rationale behind IPRs, other suggests that there exists other types of incentives “related to various types of strategic value [firms] can obtain through licensing markets or via buying and selling such IPR, i.e. by engaging in the marketplaces for intellectual property” (Andersen et al., 2010, p.35).

Patents however work differently in singular industries; “in the pharmaceutical the patent normally equals the product, and protects the extensive investment in research and clinical testing required before placing it on the market. Patent protection [for those] products is especially important compared with other industries because the actual manufacturing process is often easy to replicate and can be copied with a fraction of the investment of that required for the research and clinical testing” (Lehman, 2003, p.2).

Matters of discussion still remains on what is the optimal length and breadth (in terms of scope coverage) of the patent protection for a competing firm that would like to enter the market without infringing the IPR. A patent protection is defined to be broad in scope when it covers the main product as well as all chemical class products within the product or even associated to it. The width of a patent is an important dimension to take into

consideration especially if it can become a powerful barrier to entry for competitors, even those that bring to consumers improvements with respect to the original product. Worldwide it has been established by the WTO in 1995 that patents last 20 years starting from date of application. Twenty years might seem as long period but in this specific industry it makes perfect sense, because to test a drug and to bring it to the market it can take more than a decade.

1.5 Embrace Opportunities and Face Challenges

“It is not the strongest or the most intelligent who will survive, but those who can best manage change.”

Leon C. Megginson

The best in pharmaceutical industry is yet to come; the very nature of the industry offers endless opportunities to improve the state of the art and to establish new paradigms of drug development and distribution. “The best vehicle to be driven is on the road ahead is that of promising scientific possibilities on the wheels of novel technology but at a velocity regulated by ethics and proactive compliance” (Raddy, 2011, p.11).

As it has been stressed so far there are different forces at play that are impacting value creation while challenging the current blockbusters’ business model in the pharmaceutical industry. Namely these best and worst of times are defining the business environment and represent the conditions in place that will eventually determine the evolution towards what has been defined *Pharma 2020*.

The outlook has never been more promising on one side and more threatening on the other. Indeed, if on the one hand the industry has witnessed a rapidly strengthening scientific foundation paved by an increasing technological developments, a growing demand for medicines⁵⁹ especially in growth economies where healthcare access is improving, and the removal of impediments to free trade, on the other hand pharma is facing some enormous obstacles: market condition are getting tougher with Big Pharma’s earnings tumbling over patent cliff, harsher price policies and soaring healthcare bills; innovation productivity is declining and regulations are becoming more burdensome⁶⁰.

⁵⁹ See par. 1.1.3, The industry in numbers.

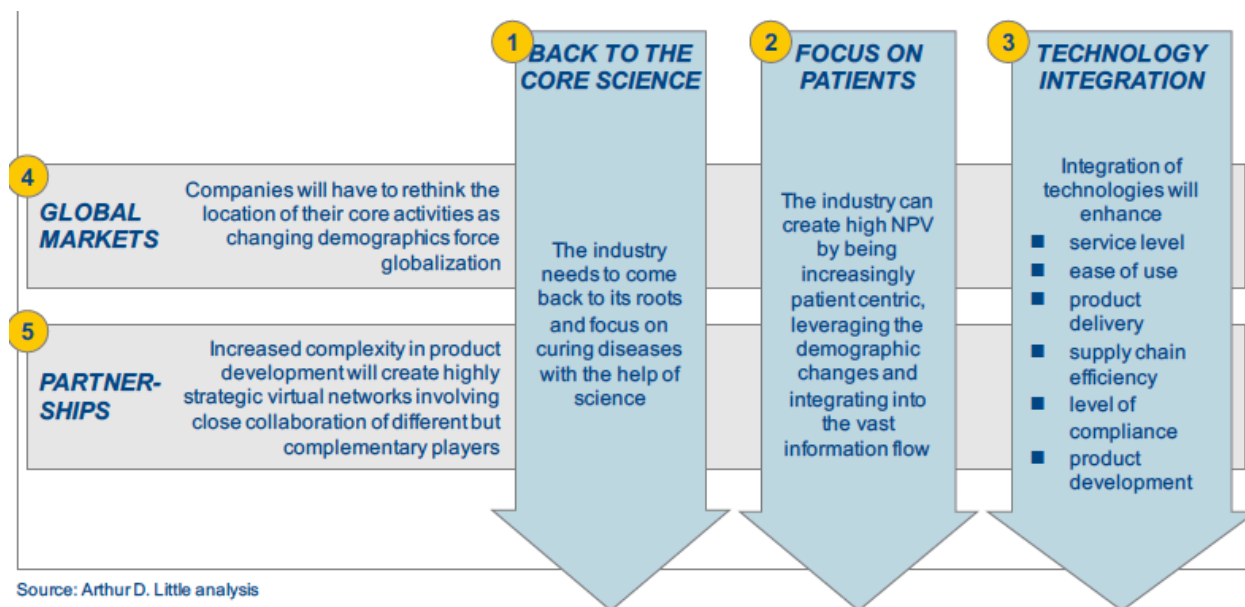
⁶⁰ PwC, *From vision to decision: Pharma 2020*, 2012.

Challenges can be overcome and turned into new business opportunities according to Arthur D. Little (2016), which suggests five key recommendations – key levers – to shape the industry’s future and have success in the new evolving healthcare landscape (Figure 13):

1. **Back to core science:** return to back to the industry’s roots and focus on curing diseases with the help of science and on a strong medical science basis. It means that in a time in which the blockbuster growth is becoming insufficient, the industry must identify a need first and then use science to answer to it. In the past, instead, companies would focus on discovering the innovative molecule first and then market it. Today we are witnessing an increase focus on personalized-medicine, developing particular niche-buster business model.
2. **Focus on patients:** the industry can create high NPV investments by being increasingly patient centric, leveraging on demographics changes. The beyond the blockbuster business model implies putting the patient right at the centre of product development in order to offer better services while avoid malpractices.
3. **Technology integration:** integrate technologies and digital solutions to supply better treatment faster. This will enable a fully integrated product offering that will enhance the service level, product delivery, the supply chain efficiency, the level of patients’ compliance as well as the overall product development. Technology integration implies moving from a fully integrated system to a virtually integrated one, in which emerging technologies will provide new and more precise cures and data will be used to optimize treatments. The rise of new technologies will increase manufacturers flexibility and improving supply chain efficiency by delivering directly to pharmacy bypassing the traditional wholesalers.
4. **Global markets:** As demographics is changing and disposable incomes as well as middle-class households are rising in pharmerging countries, companies must think to relocate their core activities in the global markets, leveraging on the current medical infrastructure’s expansion and on greater penetration of health insurance. Companies must be ready to use the global market and global resources.
5. **Partnership:** Increased complexity in product development is leading to the creation of strategic virtual networks that involve the collaboration of different but complementary players in order to accelerate success. Indeed the lack of skills and the need for greater production flexibility is increasing reliance on outsourcing; furthermore the need to ease the development process and offer more tailor-made solutions is stimulating companies to collaborate, now more than ever, with governments and payers as well as close-to-patient personnel.

These key recommendations highlights what have been identify in this chapter the key success factors (KSFs) of the industry: strong scientific base paired with efficient R&D, penetration of pharmerging markets capitalizing on increasing demand and value creation through capital investment strategies.

Figure 25 Key Recommendations to Shape the Industry Future



Source: Arthur D. Little, 2016.

Constant cutting-edge innovation is key if pharmaceutical companies want to preserve their competitive advantage in the market. Striking win-win partnerships in the industry is one way to identify rewarding prospects and pursue them so that mutual benefits are possible for all stakeholders. Collaborating with biotechnology firms could lead to new prospective of drug possibilities. The high innovative discovery proportion of biotech firms makes them ideal for sub-processes of drug development. The insightful domain knowledge that these new companies are gaining makes them suitable associates for the pharmaceutical industry. Biotech companies have a lot to offer to the industry of pharmaceuticals, for this reason they have become more attractive, providing treatments that traditional drugs can't offer such as orphan drugs⁶¹ while also benefiting from reduced competition since biosimilars still require exponentially more funding, time and regulation to develop than generics⁶².

Besides betting on innovation, pharmaceutical companies need an efficient R&D system through the implementation of information systems and predictive models and therefore greater technology integration. "Better predictive models would improve the efficiency of the drug development process by either narrowing the patient population where the drug has the best chance of success, or eliminating candidate drugs before risky and

⁶¹ Orphan drugs are medicines for rare diseases which normally affect less than 200,000 people and have become prevalent due to the high revenue streams

⁶² Grabowski H., Guha R., Salgado M., *Biosimilar Competition: lessons learned from Europe*, *Nature Review Drug Discovery*, Vol. 13, pp. 99-100, January 2014.

costly clinical trials begin” (Long & Works, 2013, p.4). Many of the top players of the industry have reorganized their R&D model to achieve stronger growth and earnings potential. In fact, following the patent cliff turmoil, organizational structures that worked in the past were no longer sufficient; Sanofi changed their organizational model in an attempt to not only reduce the complexity of R&D, but to also to become more open to external sources of innovation and partnerships, while Merck & Co. went through a \$2.5 cost saving initiative to reorganize a vertical organization to one that has a more decentralized approach and a horizontal format, so that innovation and productivity will be significantly higher⁶³.

Emerging markets are tomorrow’s source of revenues and the development of those regions makes them incredible attractive. These countries show relatively low-income levels and growing health problems, which make the market favourable to generic pharmaceutical companies. Companies worldwide are starting to realize the full potential of capitalizing on global expansion, BRIC markets continue to grow and both productions as well as competition levels will continue to rise. According to Statista, spending on medicine in pharmerging markets will rise to 372 billion dollars by the year 2018⁶⁴.

Recent trends have led pharmaceutical companies to diversify their product portfolios. During the last decade M&A and divestitures were among the most utilized strategies – and still are – to unlock fundamental changes in order to offset patent cliff, to strengthen key therapeutic areas, to increase market share in emerging markets as well as accelerate the race to develop new drugs expanding products lines and gaining competitive advantage. Nowadays the pharmaceutical industry is in a period of transition, out of the blockbusters business model typical of the ‘90s, towards a new strategy for growth in an increasingly globalized market⁶⁵. The empire building strategy utilized by management executives a decade ago has now been replaced by a new business model focused on balancing risk and opportunity through diversification. The slowing pace of drug discovery together with an intensified regulation has increased the urgency of adding new lines of business, in this context increasing reliance on partnerships, acquisitions and joint ventures has proved so far to be an effective method of funding R&D⁶⁶.

⁶³ Adeusi S.O., *Pharmaceutical R&D: An Organizational Design Approach to Enhancing Productivity*, Massachusetts Institute of Technology, Sloan School of Management, May 2011.

⁶⁴ Statista, 2014.

⁶⁵ Baum A., *New Product Generation and an Easing Regulatory Environment in Biopharmaceuticals*. Wall Street Transcript, Vol. 192(3), pp. 57-61, 2013.

⁶⁶ Baldi, F., Baglieri, D., Corea, F., *Balancing Risk and Learning Opportunities in Corporate Venture Capital Investments: Evidence from the Biopharmaceutical Industry*, Entrepreneurship Research Journal, Vol.5(3), pp.221-250, 2015.

1.5.1 How to Face Challenges Ahead

The pharmaceutical industry and in particular the so called *Big Pharma* are now experiencing the same phenomenon other industries before them have already faced: being forced to try and reinvent themselves in the face of challenges in their business environment. As once Martin Luther King once said: “the ultimate measure of a man is not where he stands in moments of comfort, but where he stands at times of challenge and controversy.” Only the firms willing to change their strategies and readapt their current products portfolio, choosing the “best jams”, will have long-term success.

Companies have responded to these challenges engaging in a variety of corporate strategies – M&A, partnerships, diversification, licensing agreements just to name a few – aimed at paving the way for future success. Mergers and acquisitions in particular are part of these changes: Merk’s merger with Shering Plough, Pfizer buyout of Wyeth and Roche’s acquisition of Genentech are just few examples of how M&A has been employed for consolidation. Johnson & Johnson, Novartis and Abbot have preferred to follow the path of diversification in other business areas while other players instead have focused strongly on expanding operations in emerging markets through strategic alliances.

In this climate of change the key to long-term success lies in building a **balanced heterogeneous portfolio**. Just like a responsible investment manager does not bet all its clients’ money only on risky assets, that only might deliver a big return, but it combines speculative investments with bread-and-butter stocks to generate a steady return, so must pharma companies constantly keep an eye on their portfolios, allocating the right amount of resources to valuable candidates while also reducing waste from R&D costs. Even though the paramount goal is clear, there is no defined path to reach it and the route each company might take will depend exclusively on their individual aims and circumstances.

2 Corporate Growth Strategies & Portfolio Management

As it has been previously analyzed, the pharmaceutical industry in last decade has been characterized by changes in the state of the art as a result of the overall economic downturn, the rising healthcare costs as well as the soaring expenditures associated with R&D, while innovation productivity continues to decline. Players in the pharma industry are facing constant arising opportunities and challenges; the blockbusters business model – on which they become so dependent on – is showing signs of weakness due to the fact that many blockbuster drugs are scheduled to go off patent and firms' portfolio pipelines must be well-prepared to replace those soon-to-be-lost earnings in order to maintain the industry historically high-growth rates.

As a response to these challenges, Big Pharma have re-evaluated their growth strategies to address these issues by laying down a series of corporate strategies such as merger and acquisitions, partnerships, diversification strategies, licensing agreements and strategic alliances. Their long-term achievements will depend on how successful those strategies will unfold in the future; hopefully looking through rearview mirror firms will realize they made the right portfolio and business decisions.

This chapter wants to give an overview at the ways in which companies have tried to modify their ways of doing business and have responded to past changes, in particular focusing on strategic options such as M&A, strategic alliances and licensing. Due to the fact that companies in this sector have to navigate in an increasingly volatile environment the management of a portfolio of strategic products is a necessary condition for long-term survival, thus playing a pivotal role for every company that aims at maintaining its competitive advantage and increasing shareholders value. In this respect, this chapter aims also at reviewing the commonly used techniques and matrices in terms of portfolio analysis, both for already marketed products as well as those still in pipeline, employed to inform firms about their own competitive position, suggest strategic options and define priorities in terms of resource allocation among the different products or business.

2.1 Corporate Strategies in the Biopharmaceutical Industry

“It is clear that you cannot stay in the top league if you only grow internally. You cannot catch up just by internal growth. If you want to stay in the top league you must combine.”

Daniel Vasella, Novartis CEO, (July,2002)

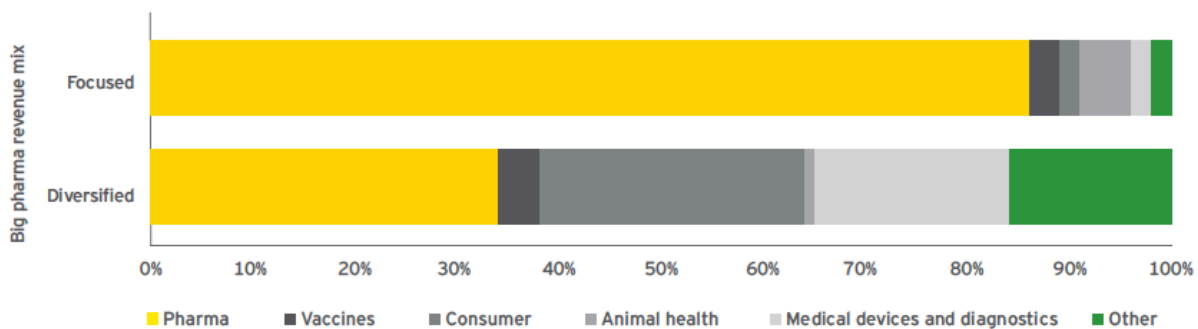
Corporate strategies put in place by companies, independently from the industry-type and the mere rationales – whether they aim at either horizontally or vertically expanding or diversifying the business – can fall into two options: *internal* or *external* growth. The former assumes that growth is based on the efforts and resources internally from the firm. Organic growth strategies are common in new product development, product-related strategies and also international expansion. The latter instead – also defined as inorganic growth – implies that growth is achieved by looking outside the firm itself, relying on relationships with third parties. Relationships can take different shades – from M&A to strategic alliance and JV, from licensing to venturing – each one has its own pros and cons and it is pursued according to the goals firms’ intent to achieve. It is generally acknowledged that growth should be fostered first and foremost with internal resources and only when these investments become economically unsustainable must then firms examine opportunities outside. Pharmaceutical companies have in the last decade preferred to look outside to fill the weak in their pipelines and spur growth.

In the midst of challenges pharma companies look at M&A and other form of strategic partnerships as the easy way out to address the problems they face. Especially when companies dispose of substantial cash flows to invest, M&A activity has been the most widely used strategy to hedge against the adverse impact of patent cliffs and the associated expected revenues’ shortfall, as well as to increase competencies and know-hows to trigger R&D growth. As the risk of revenue shortfall increases even companies with solid growth projections may pursue M&A to protect against the downside scenarios. While some companies may focus on defensive M&A, others may prefer alternatively to diversify their revenue mix away from the pharma core business in adjacent life science business areas such as vaccines, animal health or medical devices (Figure 41).

Nowadays industry outlook indicates, yesterday as today, an active biopharma deal environment as a direct consequence of the global industry’s structural shift towards externalizing R&D and in response to the intensified power exhibited by payers. Even in markets such as oncology where companies have relatively strong pricing power, continued growth might become difficult. This is why also divestiture strategies have been put in place to shed underperforming or undersized businesses while refocusing on diseases areas where companies can

compete for the leadership⁶⁷. As Fred Hassan, former CEO of Schering Plough stated in an interview in 2010⁶⁸ “large drugmakers will need to merge to fund expensive, complex areas of research such as Alzheimer’s disease. [...] One reason deals are necessary is because innovation investments are becoming larger and larger and it makes it easier when people can combine their resources to make the big deep bets that you need to make for difficult diseases.” Finding therapeutic “white space” in unmet areas may require companies to pursue higher-risk opportunities, “driv[ing] future M&A as companies compete for the best assets in key (...) areas where drug sales currently represent a smaller portion of total related healthcare costs” (EY, 2017, p.3); this win-or-go home mindset is what’s driving today’s M&A and divestiture agendas.

Figure 26 Strategic Divergences⁶⁹



Source: EY, 2017.

2.2 M&A Strategy:

M&A activity on large scale played a pivotal role in influencing the performance of the Big Pharma over the years in terms of sales’ volumes. From 1995 till 2014 the total sales value realized from the Big Pharma experienced a growth of \$297.4Bn in absolute terms – from approximately \$84Bn to \$381Bn. A MarketLine analysis estimated that such incremental value was to be attributed for 63% to the sale generate thanks to M&A activity. Diverse growth strategies impact firms’ performance, in terms of revenue generation, differently: In fact, revenues of companies that have preferred an internal growth strategy during those same period increased by 2.3 times while the performance of firms that followed an M&A strategy more than quadruplicated, increasing by 4.6 (Figure 27).

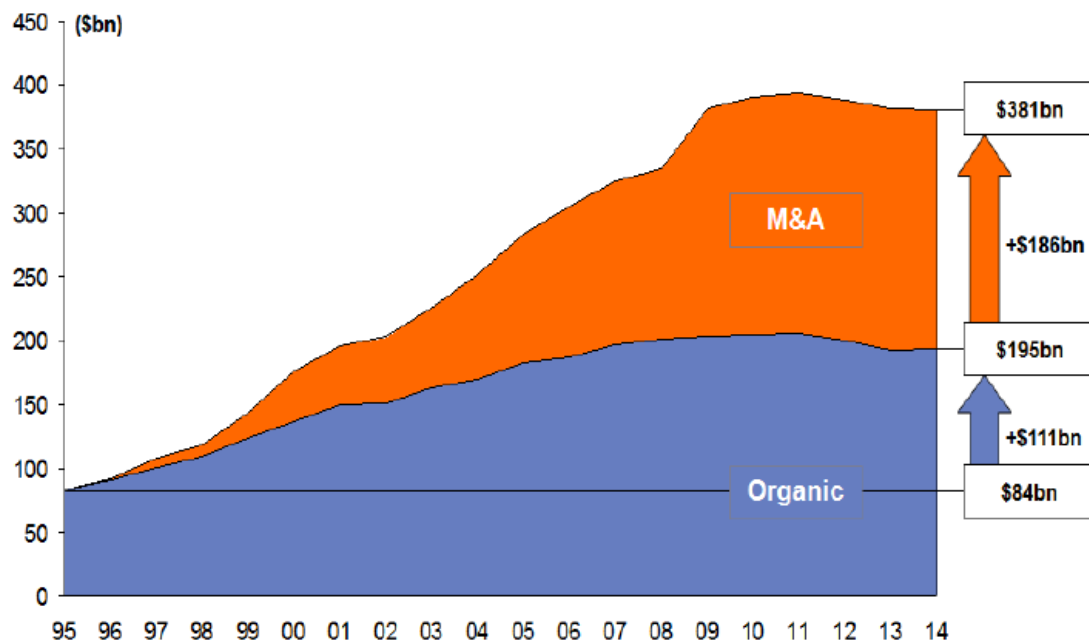
⁶⁷ EY, *M&A Outlook and Firepower Report 2017*, 2017.

⁶⁸ Pettypiece S., *Former Schering Plough CEO Hassan sees more deals among drug-makers*, Bloomberg, February 2010.

⁶⁹ Focused: companies with pharma sales greater than 70% includes: AstraZeneca, AbbVie, Merck, Eli Lilly, Novartis, Pfizer, Boehringer Ingelheim, Roche and Sanofi. Diversified: companies with pharma sales less than 50% include: Abbott, Bayer, GSK, Johnson & Johnson.

M&A activity has allowed firms to increase in scale, positively influencing the proliferation of successful blockbusters into the market, which consequently led to an upturn in revenues. Indeed, only in the time period between 2001 and 2008 sales revenue generated by major blockbusters increased with a compound annual growth rate of 11.2%⁷⁰. If on the one hand these waves of M&A transactions, oriented to acquisition of blockbusters in their pipelines, contributed significantly to the growth of the acquiring firms, on the other hand the pressing need to constantly and successfully update their product portfolios to counterbalance the off-patent risk represent one of the main weaknesses of this strategy⁷¹.

Figure 27 Revenue Generation by Big Pharma, 1995-2014



Source: E.Zoli, 2010.

In fact, because big pharma's R&D function cannot always guarantee a portfolio in equilibrium, in order to allow for a constant turnover that it is essential for a company long-term sustainability, M&A remained the easy way out, especially in a decade where pharma's main business model revolved around blockbusters. Furthermore, M&A activity allowed big pharma companies to internationalize as well as to strengthen their capabilities in terms of sales and marketing.

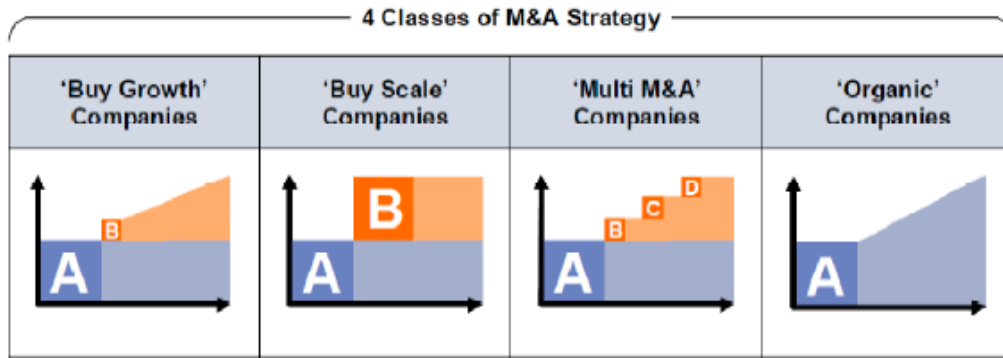
⁷⁰ Zoli, Elisa, *Prede e predatori: il ruolo chiave dell'M&A nell'industria delle Big Pharma*. Tesi di Laurea in Finanza aziendale avanzato, LUISS Guido Carli, (A.A. 2009/2010).

⁷¹ An example could be the acquisition of Wyeth by Pfizer in 2009, whose main rationale was reducing the loss and filling the hole left by Lipitor, a blockbuster product for the company responsible for 23% of total sales revenue, going off-patent.

In a study published in 2009, Datamonitor⁷² classified companies' growth strategy into four M&A classes (Figure 28):

- *Buy Growth* – companies whose M&A activity was aimed at increasing prescription sales' growth.
- *Buy Scale* – companies whose M&A deals were directed at increasing product pipeline portfolios, R&D and Marketing and Sales (M&S) capabilities.
- *Multi-M&A* – companies that engaged in more two or more acquisitions.
- *Organic* – companies that avoid M&A as core strategy.

Figure 28 Classes of M&A Strategy



Source: E.Zoli, 2010; Datamonitor, 2009.

Among the companies listed as “buy growth” there are Johnson & Johnson as well as Roche. The latter thanks to the Genentech acquisition in 2009 has boosted its sales performance by laying hands on the promising, and at that time rapidly expanding, MAB⁷³ business. Merck & Co., GlaxoSmithKline, AstraZeneca, Sanofi and Bayer AG are instead classified as “buy scale” companies; Sanofi in particular with Aventis acquisition in 2004 and thanks to other “merger of equals” has been able to acquire scale. Among the multi-M&A companies fall Pfizer, which since 2000 has performed a series of megamergers, for unprecedented deal value, in order to increment sales in the pharmaceuticals business and at the same time maintain its competitive position. Lastly but not least Eli Lilly and BMS are characterized by a low reliance on external growth strategies and have preferred to focus more on organic growth for the long-term success without relying too much on M&A activity.

⁷² Datamonitor, “Big Pharma Mega Mergers 1995-2014”, December 2009; Baines D.A., *Problems Facing the Pharmaceutical Industry and Approaches to Ensure Long Term Viability*, Master of Science in Organizational Dynamics, University of Pennsylvania, 2010.

⁷³ Monoclonal Antibodies

2.2.1 Winning with M&A: Major Deals throughout History

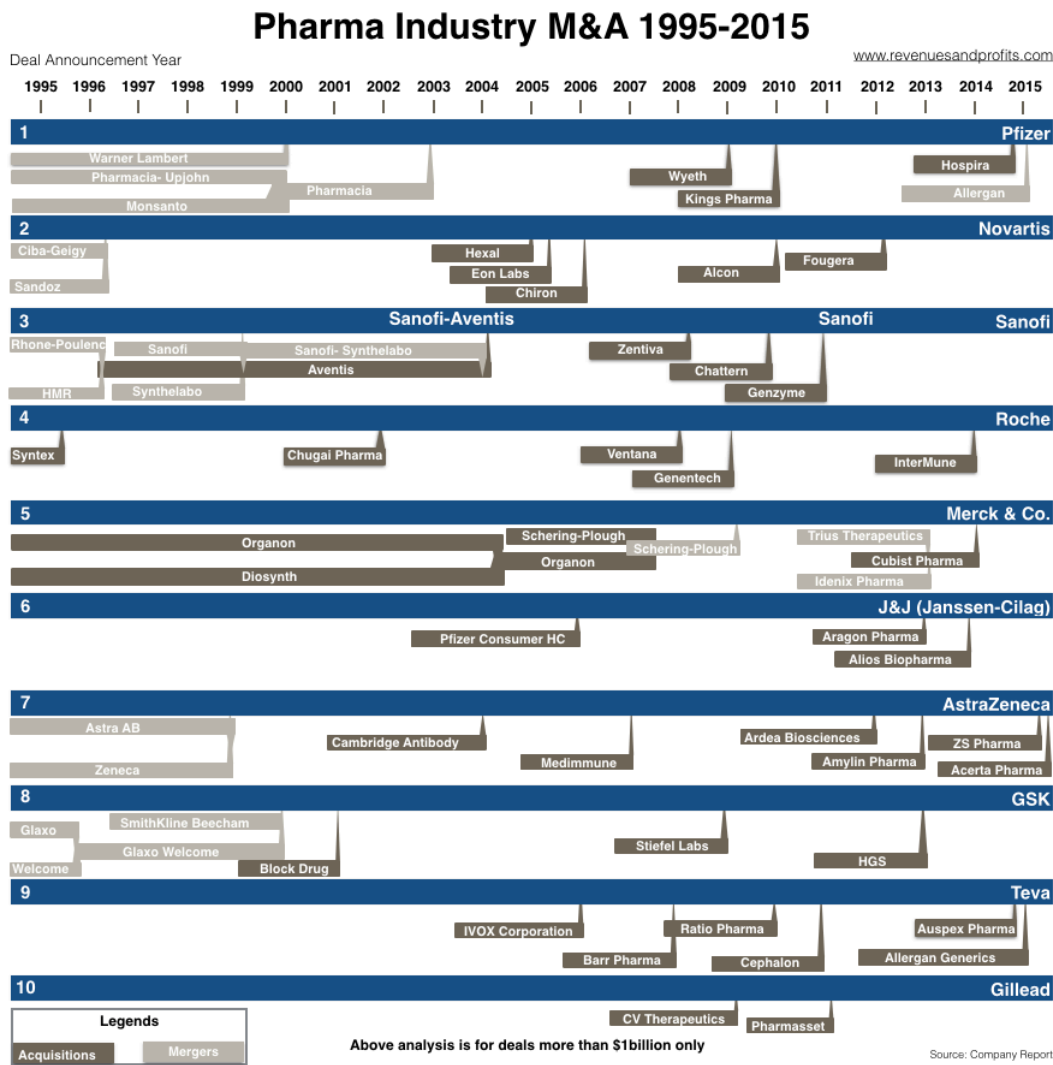
Since the end of the '80s the worldwide landscape of the pharmaceutical industry has been characterized – and it still continues to be – by mergers and acquisitions deals, which over the years have led to the rise of today's big multinational companies. In the last decades, sixty pharma companies have become just ten Big Pharma companies (Figure 29). M&A deals have played a significant role in shaping the life science industry, contributing to its constant dynamism. Mergers and acquisitions have been used as strategies to consolidate the different players in the industry with the aim of “gaining more muscle to influence regulation while simultaneously diminishing competition” (Schwartz, J. & Macomber, C., 2017, p.2). The waves of M&A deals that have occurred in the past decade are thus responsible for nowadays-pharmaceutical industry and the Big Pharma's structure. As a matter of fact, their configuration is the result of the merge of a variety of players of different sizes that since the beginning of the '90s have created a more complex organization. Companies that fit as example are: *GlaxoSmithKline*, which is the union of Glaxo, Burroghs Wellcome, Smith Kline French, Beecham, Beckman, Affymatrix, Sterling and a bunch of other smaller companies; *Sanofi* that is the result of the merge among Hoechst, Rhone Poulenc, Marion Meller Dow, Roussel Uclaf, Roger Bellon, Dakota, Rorer, Fisons, Winthrop, Connaught Labs, Meriuex and Sanofi-Synthelabo; *Pfizer* that acquired Pharmacia, Monsanto, Warner-Lambert, Parke-Davis, Kabi, Farmitalia, Surgen and Upjohn; *Johnson & Johnson*, which agglomerates more than 250 companies some of which are Alza, Cilag, Cordis, Life Scan, McNeil, Neutrogena and many more; lastly *Bristol Myers Squibb* that aroused from the merger of Bristol Myers, Squibb and Du Pont Pharmaceutical. Even though notorious firms have disappeared, the “*too big to nail*” players such as Pfizer, Roche and Merck still continue to exist.

The cyclical occurrence of M&A transactions in waves, in all industry environments, constitutes a phenomenon widely acknowledged and studied by researchers⁷⁴. The common answer to all these research work is the inability to find a sound explanation to the phenomenon. Brealey and Myers (1996) and Bruner (2006) cite M&A waves as yet one of the unresolved mystery of applied corporate finance. In an abstract from one The Economist article (1994)⁷⁵ an answer, even if trivial, is given: the upside-downs of the industry together with empire building desires from manager with financial availability are to be held responsible.

⁷⁴ William F. Shughart II and Robert D. Tollison, “*The Random Character of Merger Activity*”, The RAND Journal of Economics, Vol. 15(4),pp. 500-509, Winter 1984.

⁷⁵ The Economist Newspaper, *Making a meal of mergers, history suggests current merger activity in US may yield disappointing results*, September 1994.

Figure 29 Pharma Industry Consolidations, 1995-2015



Source: R. Vij, 2016.

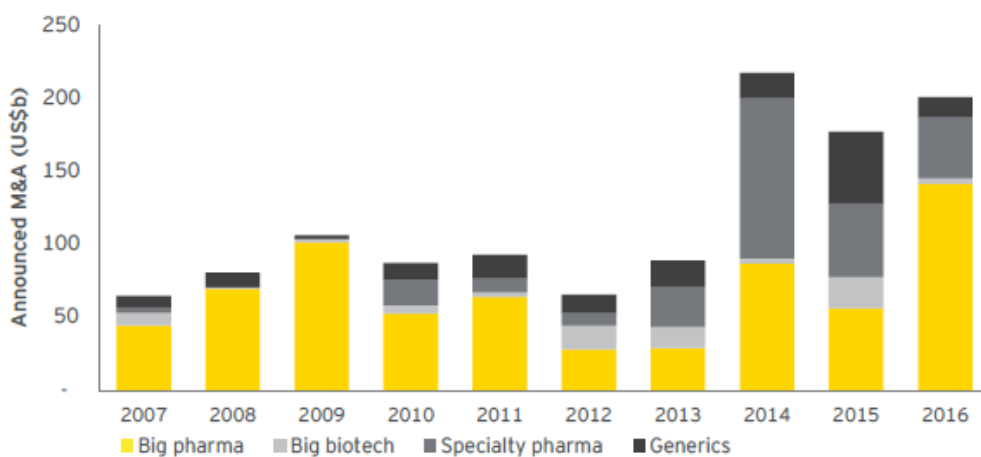
With respect to the pharmaceutical industry, the M&A waves date back to the end of the ‘80s. In particular, 1989 was a year of great changes in the industry structure, which initiated the first wave of the “megamerger” phenomenon. In that year SmithKline Beckam Corporation and Beecham Group PLC merged into SmithKline Beecham PLC; Dow Chemical acquired a majority stake in Marion Laboratories for \$2.2Bn so that Marion Merrell Dow was born; significant was also the incorporation of Squibb by Bristol-Myers. The second wave of M&A transactions occurred between 1994 and 1997 and during this period numerous deal took place to increment the concentration level in the industry. The merge between Sandoz and Ciba-Geigy for \$63Bn to form Novartis was the first actual mega-merger for deal value in the pharma history. The third wave started in 1998 when Astra merged with Zeneca. During the two years after other important multibillion deals followed: Pfizer acquired Warner-Lambert and the mega-merger between SmithKline Beecham and Glaxo Wellcome. The value

of these transactions characterized this last wave, registering a cumulative spending from 1998 till 2000 five times greater the value realized in the second wave⁷⁶. The following three years between 2001 and 2004 was instead defined from a decline in M&A in multibillion transactions, even though two of them are worth remembering: acquisition of Pharmacia by Pfizer and the merger between Sanofi-Synthelabo and Aventis.

With the start of the new millennial, M&A deals focused on biotech firms; the transactions that occurred between 2005 and 2010 highlighted three visible trends: diversification of pharmaceutical companies in medical device (e.g. J&J, Roche), generics (e.g. Novartis, Sanofi-Aventis), and diagnostics (e.g. Roche) to survive the ongoing productivity crisis and the going off-patent of some of their main blockbusters; overall consolidation of the European and Japanese pharmaceutical industry as well as greater interest towards the emerging markets – so-called pharmerging.

If the years from 2010 till 2014 showed a slowdown both in terms of volume and value of M&A transactions, recent years from 2014 to 2016 display an yearly M&A total average around US\$200Bn. EY (2017) confirms that total M&A volume in 2016 exceeded the US\$200Bn, signaling a new plateau after averaging well below US\$100Bn (Figure 30). The largest deals in 2016 highlight the strategic divergences between biopharma companies with regard to focus and diversification: Bayer proposed to acquire Monsanto to further diversify away from pharmaceuticals while strengthen its position as a top agricultural biotech; Shire seized Baxalta after a lengthy chase started in 2015 to intensify its leadership in rare diseases, while Pfizer’s acquisition previously of Allergan and then of Medivation signaled its determination to bolster its oncology portfolio.

Figure 30 BioPharma M&A 2007-2016 (EY)



Source: EY, 2016.

⁷⁶ Fortune and Business Week (2001) statistics

Figure 29 summarizes the main deals that occurred in 2015, for originators and generics pharma companies, which differ in leading drivers behind the acquisitions: the former prefer to look for pipeline and portfolio deals while the latter aim at consolidating their position in the local and global market.

Figure 31 Deals in 2015 for Originators and Generics Companies



Source: IMAP, 2015

2.2.1.1 M&A deals in biotech

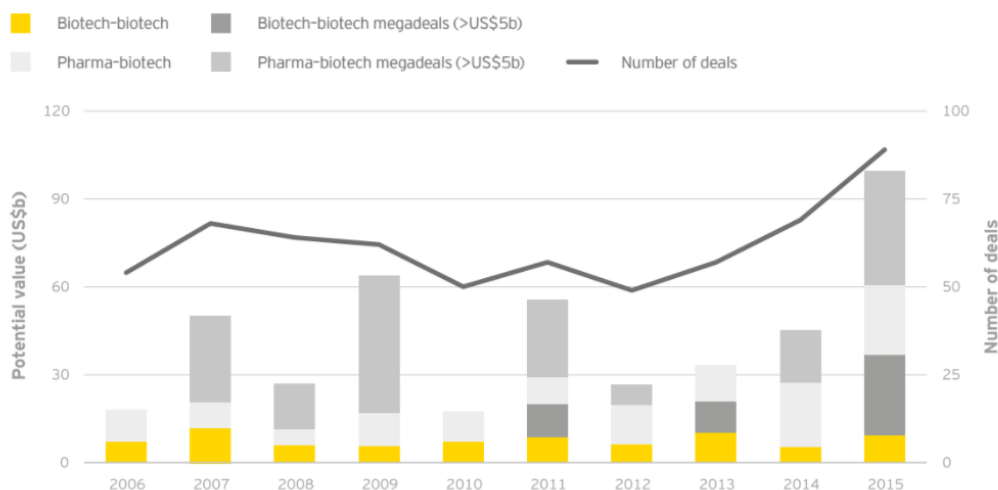
M&A transactions in the biotech sector fall in two types: the acquisition of a biotech target by a big pharma company or the merger among biotech companies.

The undisputable capability of biotech companies to develop biologic blockbusters over the years has driven pharmaceutical companies to mature partnerships at first but since the beginning of the 21st century the *modus operandi* has changed and big pharma companies have started to acquire those biotech “think tanks”. In fact, by incorporating biotech companies traditional pharmaceutical companies did not merely added to their portfolio new products but also acquired novel technologies that were otherwise too expensive to develop internally. Furthermore, since few years ago – before biosimilars came to the market – another driver in

acquiring biotech companies was the greater struggle from generics companies to replicate biologics products at the end of patent protection, thus neutralizing in part the vulnerability from patent cliffs. On the other hand also biotech companies benefited from greater financial availability as well as marketing and commercial capabilities owned by the Big Pharma. Moreover, in the absence of an IPO selling was the only exit strategy possible to recoup the investment for the venture capitalists that backup biotech. However, among the negative aspects of acquiring a biotech company to take into consideration there are the difficulties in successfully integrating different expertise in R&D as well as the diverse corporate culture. Indeed, biotech’s greater entrepreneurial mindset oppose the old-fashioned pharmaceutical companies whose the organizational structure is more business-oriented.

In 2015 AbbVie’s acquisition of Pharmacyclics, developer of Imbruvica, for US\$21Bn was the year’s largest biotech acquisition. Thanks to this transaction AbbVie gained significant and immediate presence in the oncology-hematology market. The underlying driver behind the deal was the need for Abbvie to diversify its revenue base as biosimilars threatens its autoimmune therapy Humira⁷⁷. One of the most talked buyers in 2015 was also the biopharma company Gilead Sciences, a company that has historically exercised M&A momentum to boost its product pipeline. Indeed M&A activity in that year, both in US and Europe, peaked up to new time high “as cumulative deal value jumped 120% over 2014 and at more than US\$100Bn, nearly exceeding the previous three year’s combined value. [...] Several megadeals – worth US\$5Bn or more – were responsible for a significant chunk of that aggregate total” (EY, 2016, p.66) (Figure 32).

Figure 32 US and European M&A Activity. 2006-2015



Source: EY, 2016.

⁷⁷ Only in 2015 Humira generated more than US\$14Bn sales and accounted for 61% of AbbVie’s total 2015 revenues.

M&A operations, nevertheless, are common also among biotech companies: the merger between Biogen and Idec, Amgen's acquisitions of Immune and Tularik are just an example, but many other deals have become common practice over the past decade. These deals have in fact started to consolidate the biotech segment, similarly to how it has happened in the pharma sector in the hands of major biotech; these after having become significant players in the market were looking for ways to increase their size and reach economies of scale. The main objective for those companies is therefore obtaining a sufficient increase in revenues to withstand an increasingly complex cost structure. This phenomenon highlights how biotech companies have evolved through time and may have hit their maturity stage, in which external growth options represent only way to grow. In those "merger of equals" transactions there are fewer post-deal drawbacks that in pharma-biotech deals, especially in terms of corporate culture, such to guarantee a higher probability of success.

According to EY annual biotechnology report (2016), the largest players in biotechnology have finally matured and are now facing the same capital allocation and growth questions as their traditional pharmaceutical peers, competing with them for M&A and alliances. In 2015 the number of biotech commercial leaders⁷⁸ in US and Europe was 28 (Figure 33- 34). In the US the number fell from 19 to 17 consequently to the acquisition of Cubist by Merck & Co., of Salix by Valeant and Pharmacyclics by AbbVie. At the same time The Medicines Company lost its position as commercial leader after its revenue had been eroded when Angiomax lost patent protection⁷⁹. The biotech-biotech M&A metric was pushed to all-time highs by Celgene's acquisition of Receptors for US\$7.2Bn and Alexion's acquisition of Synageva for US\$8.4Bn, signaling high competition for the kinds of assets only Big Pharma might have been able to acquire in the past.

Nowadays outlook is the age of strategic deal making and "portfolio deals" (Figure 35) – selling critical business to better suited players to own and manage them as well as looking for critical portfolios to acquire – and Novartis clearly set the example in the industry in 2015. The multiple swaps between Novartis and GSK and Eli Lilly, which strengthened Novartis' position in oncology and GSK's in vaccines while relieving Novartis of its animal health business unit in favor of Eli Lilly. The transaction left Novartis focused on the less complex, more competitive and high-profit parts of the conglomerate. "In a phase where many players [...] still believe that 'bigger is just better', more sophisticated companies realize that only a strong position in the relevant market will secure the future" (IMAP, 2016). More than any other time in the past, "big pharma companies have the firepower⁸⁰ advantage necessary to execute the acquisitions they require to bolster revenue and drug pipeline. And more than any other time [...], those deals are necessary. Big pharma and biotech's race for inorganic

⁷⁸ Defined as the companies with at least US\$500Mn in revenue.

⁷⁹ EY, *Biotechnology Report 2016: Beyond borders Returning to Earth*, 2016.

⁸⁰ According to EY the Firepower index measures a company's ability to do M&A based on the strength of its balance sheet. Company's market capitalization, cash equivalents and debt capacity provide the firepower for deals.

growth has intensified as payers continue to push back on price increases for older drugs and dampen the growth trajectory of newer therapies, especially in increasingly crowded disease areas” (EY, 2017, p. 2).

Figure 33 US Commercial Leaders, 2010-2015

2010	2011	2012	2013	2014	2015
14 companies	16 companies	16 companies	17 companies	19 companies	17 companies
Alexion	Alexion	Alexion	Alexion	Alexion Pharmaceuticals	Alexion
Amgen	Amgen	Amgen	Amgen	Amgen	Amgen
Amylin	Amylin	Acquired by Bristol-Myers Squibb			
Biogen	Biogen	Biogen	Biogen	Biogen	Biogen
Organic growth		BioMarin Pharmaceutical	BioMarin Pharmaceutical	BioMarin Pharmaceutical	BioMarin Pharmaceutical
Bio-Rad Laboratories	Bio-Rad Laboratories	Bio-Rad Laboratories	Bio-Rad Laboratories	Bio-Rad Laboratories	Bio-Rad Laboratories
Celgene	Celgene	Celgene	Celgene	Celgene	Celgene
Organic growth					Cepheid
Cubist	Cubist	Cubist	Cubist	Cubist	Acquired by Merck & Co.
Organic growth					Emergent BioSolutions
Gen-Probe	Gen-Probe	Acquired by Hologic			
Gilead Sciences	Gilead Sciences	Gilead Sciences	Gilead Sciences	Gilead Sciences	Gilead Sciences
IDEXX Laboratories	IDEXX Laboratories	IDEXX Laboratories	IDEXX Laboratories	IDEXX Laboratories	IDEXX Laboratories
Illumina	Illumina	Illumina	Illumina	Illumina	Illumina
Organic growth				Incyte Corporation	Incyte Corporation
Life Technologies	Life Technologies	Life Technologies	Life Technologies	Acquired by Thermo Fisher Scientific	
Organic growth				Medivation	Medivation
Organic growth			Myriad Genetics	Myriad Genetics	Myriad Genetics
Organic growth				Pharmacylics	Acquired by AbbVie
Organic growth		Regeneron Pharmaceuticals	Regeneron Pharmaceuticals	Regeneron Pharmaceuticals	Regeneron Pharmaceuticals
Organic growth	Salix Pharmaceuticals	Salix Pharmaceuticals	Salix Pharmaceuticals	Salix Pharmaceuticals	Acquired by Valeant
Organic growth		The Medicines Company	The Medicines Company	The Medicines Company	Decline in sales
United Therapeutics	United Therapeutics	United Therapeutics	United Therapeutics	United Therapeutics	United Therapeutics
Organic growth	Vertex Pharmaceuticals	Vertex Pharmaceuticals	Vertex Pharmaceuticals	Vertex Pharmaceuticals	Vertex Pharmaceuticals
Organic growth	ViroPharma	Decline in sales			

Source: EY, 2016.

Figure 34 EU Commercial Leaders, 2010-2015

2010	2011	2012	2013	2014	2015
8 companies	8 companies	9 companies	9 companies	9 companies	11 companies
Actelion	Actelion	Actelion	Actelion	Actelion	Actelion
Elan Corporation	Elan Corporation	Elan Corporation	Acquired by Perrigo		
	Organic Growth and merger with Elan Drug Technologies in 09/2011		Alkermes	Alkermes	Alkermes
				Organic growth	BTG
Eurofins Scientific	Eurofins Scientific	Eurofins Scientific	Eurofins Scientific	Eurofins Scientific	Eurofins Scientific
				Organic growth	Horizon Pharma
Ipsen	Ipsen	Ipsen	Ipsen	Ipsen	Ipsen
	Organic growth and relocation from USA to Ireland	Jazz Pharmaceuticals	Jazz Pharmaceuticals	Jazz Pharmaceuticals	Jazz Pharmaceuticals
Meda	Meda	Meda	Meda	Meda	Meda
Novozymes	Novozymes	Novozymes	Novozymes	Novozymes	Novozymes
QIAGEN	QIAGEN	QIAGEN	QIAGEN	QIAGEN	QIAGEN
Shire	Shire	Shire	Shire	Shire	Shire

Source: EY, 2016.

Figure 35 Examples of Portfolio Deals: Selling and Buying Business Units, 2014-15

WHEN	DEAL	SIZE	RATIONALE
DEC 15	Sanofi animal health and Boehringer Ingelheim's consumer health.	US\$ 19.7bn	Boehringer had been looking for a solution for its OTC division for some time and strengthening its core animal health franchise makes sense.
DEC 15	AstraZeneca acquiring Takeda's respiratory business, including 200 staff.	US\$ 575m	Takeda was sub-critical in respiratory treatments which in turn composes one of three core areas for AZ (see further deals below).
NOV 15	Astellas selling its global dermatology business to LEO Pharma.	US\$ 724m	Gives dermatology specialist LEO more products (atopic dermatitis, acne and skin infections) and access to China and Russia, while Astellas can use funds to accelerate innovation in its core areas.
JUL 15	Boehringer Ingelheim exiting US generics by selling Roxane to Hikma.	US\$ 2.7bn	Hikma massively increases foothold as one of the key generic players in the USA, becoming sixth largest generics provider. Boehringer can focus on its innovative platform.
JUL 15	Teva buys Allergan's generics drug business.	US\$ 40.5bn	Divesting the generics business makes Allergan a pure originator – and attractive target for Pfizer.
JUN 15	Baxter to spin-off its biopharmaceutical business.	US\$ 17.9bn	Baxter spin-offs its biopharma business unit newly called Baxalta, which then becomes an attractive target for Shire. Baxter to focus its core business around hospital supply.
MAY 15	SigmaTau divests OncoSpar to Baxter / (Baxalta).	US\$ 900m	Divesting the oncology business and merging its European sales with Alfa Wassermann splits SigmaTau in two parts.
JUL 14	AstraZeneca acquires Almirall's respiratory business.	US\$ 875m	Almirall had great hopes for its respiratory drugs, but found competition was too strong and sold it to AstraZeneca, for which respiratory is one of three core businesses.
JUL 14	Mylan acquires Abbott's ex-US developed markets generics business.	US\$ 5.3bn	Almost pure generic player Mylan is a better owner for slow-growing and low-margin generic drugs in established markets than Abbott – who is in MedTech and hospital supply.
MAY 14	Merck & Co. sells their OTC drugs to Bayer.	US\$ 14.2bn	Bayer's stated goal to become the world's largest OTC supplier meant it had to buy the legacy drugs from Merck, most of them former Schering brands.
APRIL 14	Novartis vaccine business to GSK. (October: influenza business to CSL).	US\$ 5.3bn US\$ 275m	In a big strategic reshuffle, Novartis and GSK combined their vaccine businesses (now owned by GSK), oncology division (now owned by Novartis) and OTC drugs (pooled in a JV), while Novartis sold its animal health business to Eli Lilly. Result: all units with substantially better relative market shares.
APRIL 14	Novartis and GSK pool OTC businesses in 36.5: 63.5 JV.	n/a (US\$ 10.1bn combined revenue)	
APRIL 14	Novartis acquires GSK's oncology division.	US\$ 14.5bn	
APRIL 14	Novartis sells its animal health business to Eli Lilly.	US\$ 5.4bn	

Source: IMAP, 2015

2.2.2 Rationales for M&A

M&A processes are undeniably complex to implement with low rate of success, mainly because of the ridiculously high premium paid by the acquiring firm and ineffective post-deal integration. In light of those risks, then why major pharmaceutical companies continue to opt for an external growth strategy, such as M&A?

Understanding the reasons that lead a company to engage in an M&A transaction has been the focus of several academia research studies. Since M&A represent the most relevant strategic move in the context of external growth, in terms of financial means but also long-term commitments, a careful assessment of those reasons is necessary in order to gain insights on the potential value and the synergies to be realized after the deal is made. Literature research have indeed highlighted how M&A turns out often to be unsuccessful, specifically how the acquirer seems to benefit less, even though it was the party that proactively looked for and engaged in deal⁸¹. Understanding the motives driving the transaction is a pivotal step towards the accomplishment of a successful transaction.

Based on a literature review, rationales have been classified in intra-firms reasons and market-driven reasons; the former agglomerates all the reasons driven by firms' strategy and resources and capabilities involved in the deal. The latter, instead, are driven by factors connected to the industry and the general economic environment, which are often cited as an explanation for the M&A waves of the last hundred years⁸².

2.2.2.1 Intra-Firms Reasons for M&A:

2.2.2.1.1 Synergies

One of the most cited reasons for M&A is the exploitation of synergies by joining resources and capabilities⁸³ among the companies involved in the transaction. It was first Ansoff (1965) to introduce the concept of synergies defined as “the whole is greater than the sum of the parts”. In his opinion, the interaction

⁸¹Porter, M. E. (1987). *From competitive advantage to corporate strategy*. Harvard business review, 65, 43-59.; Ravenscraft, D. J., & Scherer, F. M. (1989). *The profitability of mergers*. International journal of industrial organization, 7(1), 101-116.; Tichy, G. (2001). *What do we know about success and failure of mergers?*. Journal of Industry, Competition and Trade, 1(4), 347-394; Cartwright, S., & Schoenberg, R. (2006). *Thirty years of mergers and acquisitions research: Recent advances and future opportunities*. British Journal of Management, 17(S1), S1-S5; McKinsey and Company (2010). *Perspectives on Merger Integration*.

⁸² Bruner, R. F. (2004) *Applied Mergers and Acquisitions*. Hoboken, NJ: John Wiley & Sons

⁸³ Trautwein, F. (1990). *Merger motives and merger prescriptions*. Strategic Management Journal, 11(4), 283-295; Damodaran A.,(2005). *The Value of Synergy*, Stern School of Business, New York.; Lenz, R. (2008). *The Logic of Merger and Acquisition*. Pricing. University Library of Munich, Germany; DePamphilis, D. (2011). *Mergers, Acquisitions, and Other Restructuring Activities*, 6th Edition. Academic Press.

and joint utilization of two firm's resources and capabilities could give rise to higher value compared to a situation in which the two firms were to act independently. Ansoff (1965) identify four different types of synergies: *sales synergies* – through the common usage of distribution channel and warehousing; *operating synergies* – through higher capacity utilization and faster progression along the learning curve; *investment synergies* – through R&D transfer across products; *managerial synergies* – through managerial capabilities transfer. Chatterjee (1986) proposed a further classification of synergies: cost of capital related (financial synergy), cost of production related (operating synergy) and price related (collusive synergy). More recently, both Damodaran (2005) and DePamphilis (2011) considered only operational – identified as economies of scale and scope, greater pricing power, know-how transfer – and financial synergies – e.g. increase debt capacity, lower cost of debt and tax benefits. Instead, Bruner (2004) opted for a classification of synergies in two distinct classes: synergies from “*assets in place*” and synergies “*from real options*”. The former includes synergies deriving from management's ability to exploit existing opportunities such as cost reduction, revenue enhancement, asset reduction and financial synergies. The latter, on the other hand, comprises synergies whose exploitation depends on the occurrence of certain events and are, by nature, uncertain; these can be growth options, exit options, options to defer and switch options synergies.

Nevertheless, despite being one of the most cited reasons for M&A, synergies overestimation and missed exploitation are considered also among the causes for failure in M&A transactions⁸⁴.

2.2.2.1.2 Economies of Scale and Scope

Economies of scale and scope are a major source of operating synergies, usually leading to cost reduction savings⁸⁵. By exploiting joint activities and resources - i.e. production, marketing and sale, finance as well as facilities and distribution channels – merged firms can spread fixed costs across an increased number of units produced⁸⁶ and at the same time it can further cut its unit costs by progressing faster on its learning curve. According to Porter (2008), by leveraging on these competitive advantages, merged firms can earn higher margin and decide whether to differentiate its products from competition (differentiation strategy) or become a cost leader by setting lower prices than competition (cost leadership strategy).

⁸⁴ KPMG (1999). *Unlocking shareholder value: The keys to success. Mergers and Acquisitions*-Global Research Report; Chatterjee, S. (2007). *Why is synergy so difficult in mergers of related businesses?*. *Strategy & Leadership*, 35(2), 46-52.; KPMG (2011). *A new dawn: good deals in challenging times*. Mergers and Acquisitions Global Research Report.

⁸⁵ Damodaran A.,(2005). *The Value of Synergy*, Stern School of Business, New York; DePamphilis, D. (2011). *Mergers, Acquisitions, and Other Restructuring Activities*, 6th Edition. Academic Press; Gomes, E., Weber, Y., Brown, C., & Tarba, S.Y. (2011). *Mergers, acquisitions and strategic alliances: Understanding the process*. New York: Palgrave.

⁸⁶ Shepherd, W. G., & Shepherd, J. M. (2003). *The economics of industrial organization*. Waveland Press.

2.2.2.1.3 Economies of Vertical Integration

Economies of vertical integration can also be considered a source of operational synergies, since from backward or forward integration along the value chain cost reductions can arise⁸⁷. A merged firm can indeed achieve substantial savings enjoying lower or null transaction costs as well as lower input prices, resulting from the elimination of intermediaries along the value chain in the case of backward integration. In case of forward integration the company could afford to sell products at lower market prices. Vertical M&A can also lead to an increased assurance of supply and demand, by lowering uncertainty and increasing bargaining power.

2.2.2.1.4 Acquisition of Complementary Assets

As the industry continues to evolve firms struggle to find efficient and fast solutions to keep growing and developing new products. Therefore, even if internal growth strategies may be safer, they usually turn out to be too long to be implemented. For this reason, when faced with the dilemma “build or buy”, companies usually prefer the latter option and pursue external growth⁸⁸. Through M&A firms quickly access the resources they lack that other firms own, i.e. specific know-hows, brand recognition, financial means, distribution channels, new technologies or IP rights. The acquisitions of small med-tech and biotech companies by large pharmaceutical firms is an effective example of how big pharma have chosen M&A as a substitute of R&D over the past⁸⁹. Through these transactions big pharma companies acquired innovative IP rights, by laying hands on new products to enrich their pipelines without recurring to the long development periods, while biotech on the other hand benefited from large financial and commercial resources.

2.2.2.1.5 Business and Geographic Diversification

M&A allows firms to diversify not only across activities, but also markets and geographical areas. Diversification through M&A has two main justifications: one is the possibility to exploit financial synergies aiming at lowering the cost of capital by bringing together unrelated businesses since the volatility of the cash flow decreases⁹⁰; the other is the possibility to diversify in emerging markets to rely on new potential sources of

⁸⁷ Arrow, K. J. (1975). *Vertical integration and communication*. The Bell Journal of Economics, 173-183.; Gomes, E., Weber, Y., Brown, C., & Tarba, S.Y. (2011). *Mergers, acquisitions and strategic alliances: Understanding the process*. New York: Palgrave.

⁸⁸ Balakrishnan, S. (1988). *The prognostics of diversifying acquisitions*. Strategic Management Journal, 9(2), 185-196.; Shelton, L. M. (1988). *Strategic business fits and corporate acquisition: Empirical evidence*. Strategic Management Journal, 9(3), 279-287..

⁸⁹ Pisano, G. P. (1991). *The governance of innovation: vertical integration and collaborative arrangements in the biotechnology industry*. Research Policy, 20(3), 237-249; Hitt, M. et al. (1996). *The market for corporate control and firm innovation*. Academy of management journal, 39(5), 1084-1119.; Bower, J. L. (2001). *Not all M&As are alike--and that matters*. Harvard business review, 79(3), 92-101.

⁹⁰ DePamphilis, D. (2011). *Mergers, Acquisitions, and Other Restructuring Activities*, 6th Edition. Academic Press.

returns. There is an ongoing empirical debate, however, on which type of diversification - whether related or unrelated – brings higher shareholders value, and on whether they create or destroy value at all⁹¹.

Firms are willing to geographically expand their business because they aim at balancing and spreading the source of their revenues, so ultimately to reduce risk and foster growth. Even though cross-border M&A is not the only alternative to enter foreign markets, it is becoming a widespread mode of entry for internationalization purposes⁹². In an international context, M&A represent a costly and risky option due to the integrations issues that might arise in the deal's aftermath. Nevertheless, it ensures quick access to complementary resources such as country-specific knowledge and local network. Figure 30 summaries the different motives why firms may opt for cross-border M&A.

2.2.2.1.6 Market Power

According to numerous studies⁹³, companies undertake M&A to increase market power even though evidence are mixed since many also claim that firms do not oftensignificantly benefit from the position achieved⁹⁴. Firms that reason in this way usually aim at reducing competition, gaining a stronger leadership position in the market, while potentially setting higher barriers to entry. Chatterje (1986) defined the advantages resulting from the merger of two or more competitors as collusive synergies.

⁹¹ Rumelt, R. P. (1974). *Strategy, structure and economic performance*. Boston, Massachusetts: Harvard Business School Press; Singh, H., & Montgomery, C. A. (1987). *Corporate acquisition strategies and economic performance*. *Strategic Management Journal*, 8(4), 377-386; Lubatkin, M., & Rogers, R. C. (1989). *Diversification, systematic risk, and shareholder return: A capital market extension of Rumelt's 1974 study*. *Academy of Management Journal*, 32(2), 454-465.

⁹² Andersen, O. (1997). *Internationalization and market entry mode: A review of theories and conceptual frameworks*. *MIR: Management International Review*, 27-42; Brouthers, K. D., & Brouthers, L. E. (2000). *Acquisition or greenfield start-up? Institutional, cultural and transaction cost influences*. *Strategic Management Journal*, 21(1), 89-97; Shimizu, K., Hitt, M. A., Vaidyanath, D., & Pisano, V. (2004). *Theoretical foundations of cross-border mergers and acquisitions: A review of current research and recommendations for the future*. *Journal of International Management*, 10(3), 307-353.

⁹³ Trautwein, F. (1990). *Merger motives and merger prescriptions*. *Strategic Management Journal*, 11(4), 283-295. Kim, E. H., & Singal, V. (1993). *Mergers and Market Power: Evidence from the Airline Industry*. *American Economic Review*, 83(3), 549-69; Gomes, E., Weber, Y., Brown, C., & Tarba, S.Y. (2011). *Mergers, acquisitions and strategic alliances: Understanding the process*. New York: Palgrave.

⁹⁴ Eckbo, B. E. (1983). *Horizontal mergers, collusion, and stockholder wealth*. *Journal of Financial Economics*, 11(1), 241-273; Fee, C. E., & Thomas, S. (2004). Sources of gains in horizontal mergers: evidence from customer, supplier, and rival firms. *Journal of Financial Economics*, 74(3), 423-460; Shahrur, H. (2005). *Industry structure and horizontal takeovers: Analysis of wealth effects on rivals, suppliers, and corporate customers*. *Journal of Financial Economics*, 76(1), 61-98.

Figure 36 Motives for M&A

		Acquiring Company	
		Existing Products	New Products
Target Company	Existing Markets	Market penetration: acquire complementary assets to expand current market share	Product Development: to acquire new capabilities within current market
	New Markets	Market Development: Expand in new markets by relying on existing competencies.	Diversification: To add new products in new markets

Source: Elaborated from E. Zoli, 2010.

2.2.2.2 Market-Driven Reasons for M&A:

2.2.2.2.1 R&D Productivity Decline

In the context of the pharmaceutical industry, the main issue big pharma have to face since few years ago was the slowdown of R&D productivity. Such trend was visible looking at reduction in the number of New Molecular Entities (NMEs) FDA approvals that successfully entered the market⁹⁵ since the ‘90s. The reduction in successful drug approval by FDA, however, does not led to a subsequent decrease in R&D investments – which on the contrary have since kept rising. Among the plausible causes for the low productivity Zoli (2010) identified both the increasing cost of developing a new drug – which augmented x8.2 times since the beginning of the ‘90s – and the pressures from regulatory authorities. For those market-related reasons big biopharma companies have been oriented towards M&A to offset sales reduction and operating margins erosion. Lower R&D productivity has impacted pharma companies’ pipelines, such that companies have started to focus on launching merely “follow-up” drugs to support the already existing blockbusters. The reduction of NMEs was in fact a mere reflection of the sterile pipelines that firms tried to compensate by acquiring biotech companies to gain access to new innovative drugs.

⁹⁵ FDA products approval reached its lowest in 2007. Since then it started to grow again until in 2015, for the second consecutive year, more than 40 new drugs were approved by the FDA, (EY, 2016).

2.2.2.2.2 Patent Cliff and Generics Threat

The pharmaceutical industry highly depends on intellectual property rights (IPRs) – namely patents – that aim at protecting new innovative drugs. Therefore, patent expiry and the consequent loss of exclusivity rights in marketing blockbusters has caused, and still does, big pharma to worry. Revenue erosion risk following declining market shares due to generics entering in the market is indeed one of the main concerns for pharma companies. The high vulnerability is due to an excessive dependence on a “blockbuster business model” and a reduction in the period of exclusivity in the market – used to recoup costs – from the time of the first mover advantage and the entry of follow-on drugs. At time of the loss of exclusivity (LoE) pharmaceuticals are impacted by a rapid loss in their commercial value⁹⁶, consequence of the reduction of both volumes and price, leading to an average revenue decline of 50% after LoE. In the next five years nine out of the top 20 drugs⁹⁷ will go off patent in the US. For those reasons, pharma companies have proactively used M&A – and will presumably continue to do so – as an instrument to protect revenues threaten by LoE and maintain their product portfolio balanced.

2.2.2.2.3 Broaden Product Portfolio

M&A has been also an excellent tool to broaden and improve pipelines, besides adding new expertise and diversify the business in new therapeutic areas. It is fundamental for companies in this sector to strike for – and later maintain – a balanced pipeline in terms products in different study and development phases as well as in diversified business areas in order to avoid negative impacts on firms’ bottom line. Entry in new therapeutic areas – such as oncology or rare disease areas – as well as strengthening in those already present have been among the most frequently reason for M&A wave of the last decade. Nevertheless acquisitions have also been useful to manage the drug life cycle and acquire capabilities and know-hows.

In recent years, leading pharmaceutical companies have turned to mergers and acquisitions to as a strategy to spur growth, shopping not only for products but also for technology and even competitors to enhance R&D pipelines and boost the revenue bottom line. Conventional wisdom believes that M&A, especially in the healthcare sector, is like a rolling dice: it’s hard to guarantee success due to the technical, regulatory and commercial risk involved⁹⁸. Merging cultures, maintaining key researchers and sustaining an innovative environment are just a few challenges faced by the acquiring company⁹⁹. Even though, several factors must be

⁹⁶ According to Zoli (2010) generics subtract approximately 30% of branded products’ volumes in the first year after LoE and subsequently erode another 15% in the second year. Furthermore, ethical drugs prices are cut off 15% to compete with generics.

⁹⁷ The top 20 drugs are manufactured by 14 companies and account for a total 10% of global prescription drug market in 2016. Total revenue generate by those products was estimated to be US\$ 0.128 trillion. (Dezzani, 2017)

⁹⁸ Bain & Company, *Six ways to make healthcare deals work*, Healthcare M&A collection, June 2010.

⁹⁹ Cohen et al., *Strategic alternatives in the pharmaceutical industry*, Managerial Challenges in the Pharmaceutical, Biotech, and Medical Device Industries, Kellogg School of Management.

present to contribute to the deal success, what can firms do to attain a high degree of success in implementing an M&A strategy? According to a research paper by Bain & Co.¹⁰⁰ the deals that will most likely succeed are those that by acquiring assets and skills strengthen the core business. When “merger and acquisition results in a robust pipeline of innovative, clinically differentiated products [then] such deals hit the jackpot [and] create value for all stakeholders”, offsetting the headwinds pharma companies face. One thing is sure as companies keep growing larger they simply need to merge to meet growth expectations. “Thus, consolidation turns out to be a mixed blessing: bringing the benefits of scale and diversification of risk, but also creating a monster of outsized growth expectations that must be constantly appeased. [...] Certainly in the short term merged do bolster pipelines, (...) but the answers are still very mixed as to whether, at the end of the day, these present long-term results.” (Cohen et al., p.13)

2.3 Beyond M&A: A Kaleidoscope of Corporate Strategies

The debate is still ongoing regarding what is the best approach for long-term viability. As Andrew Jack¹⁰¹ once wrote in article on the FT in 2009¹⁰²: “rarely in the field of pharmaceuticals have so many companies adopted such varied strategies in order to survive the intensifying structural pressures in their industry”. The problem is that there is not one magic solution guaranteed to work. To compete in such rapidly evolving environment, biopharma companies must be able to assemble the right capabilities and know-hows and to achieve this outcome business development is key. Strong external relationships and partnering are also the secret for building the right portfolio of assets and “collaboration to gain access to early innovation has long been a mainstay for pharmaceutical companies” (J. Orloff, EY interview transcript, 2016, p.60).

2.3.1 Strategic Alliances

Other corporate strategies may become more appealing than M&A and can be leveraged by pharma companies in order to bring continuous innovations to the market. In many cases M&A has failed to deliver the

¹⁰⁰ See note 79.

¹⁰¹ Andrew Jack is multiple award winning journalist, who has been writing for the Financial Times since 1990 and who specialized in health and pharmaceuticals since 2004.

¹⁰² A. Jack, *Pharma split on nature of merger as kill or cure*, Financial Times, March 2009.

much desired productivity gains, significantly increasing the importance of strategic alliances. In demonstrating the rising prominence of strategic alliances Lam (2004)¹⁰³ observed that only between 1997 and 2002 the twenty top pharmaceutical companies formed more than 1,500 alliances with biotech companies. At the same time also Shalo (2004)¹⁰⁴ suggested that co-developed products were more likely to be commercialized than those developed by a single entity. Companies have preferred to form alliances in the belief that independence foster innovation. Effective strategic alliances are, indeed, used by big companies to sign up with smaller ones to tap into their cutting-edge research and entrepreneurial energy. On the other hand small companies look for the deep pockets to insure their short-term survival and the massive distribution network only big partners can afford. In short, both parties in alliance like the fact they can start a relationship without tying the knot forever; they result in less risky, less costly and more flexible ways to acquire capabilities¹⁰⁵.

Eli-Lilly, Merck and Roche¹⁰⁶ fit as successful examples; The former has invested in a sound alliance management process in an attempt to increase the odds of success¹⁰⁷; Merck instead throughout a business development transformation has since 2001 risen its partnership transactions to almost 80% and it has actively engaged in co-promotion for some of its products¹⁰⁸. The latter instead represents the exception to the rule on how a successful alliance has led to an acquisition with Genentech. In 1990 Roche bought 10% of Genentech for US\$490Mn, giving them a 60% stake and control. The agreement also gave Roche access to Genentech's Phase II products, with the option to decide whether the product or not. If Roche did took the product, they were bound to pay 50% of the R&D costs to date, the registration costs outside US as well as royalties on sales outside United States. In the way it was structured the alliance implied that Genentech maintained its independence, benefitting from much desired funding while letting the management focus on core business rather than raising capital. Roche on the other hand obtained ownership of an entrepreneurial company without fear of oppressing innovation, gaining access to an innovative product pipeline to market outside US.

Similarly to the impressive growth witnessed by biotech-biotech M&A, also intra-biotech alliances witnessed an all-time high values, doubling from 2014 to 2015 and reaching US\$20.9Bn¹⁰⁹. According to EY report (2016) this record suggested that, on one side the industry's largest biotech are nowadays regularly

¹⁰³ Lam M.D., *Dangerous Liaisons*, Pharmaceutical Executive, May 2004, Vol. 24(5) pp. 72.

¹⁰⁴ Shalo S., *The Art of the deal*, BioPartnerships – A Pharmaceutical Executive and Biopharma International Supplement, October 2004, pp.8-16.

¹⁰⁵ Fisher L.M., *How strategic Alliances Work in Biotech*, Strategy+Business, Winter 1996, Issue 2.

¹⁰⁶ In 2009 Roche completed its acquisition of Genentech, owning 100% stake in the biotech. More details on ch.3.

¹⁰⁷ Gueth, A. (2001). *Entering into an alliance with big pharma*. Pharmaceutical Technology, 25(10), 132-138.

¹⁰⁸ Bernard S., *Back to Pharma future*, BioPartnerships – A Pharmaceutical Executive and Biopharma International Supplement, pp.6-7, October 2004.

¹⁰⁹ EY, *Biotechnology Report 2016: Beyond borders Returning to Earth*, 2016.

competing with big pharma, both in terms of capital and cultural fit, to become ideal partners for smaller biotech. On the other hand, it clearly underlines the fact that big biotech have reached the same growth challenges as their pharma counterparts, making them avid dealmakers as well. Much of the alliances, it is shown in the report, focused on technologies or products connected to gene editing, gene therapy or immune-oncology. Two alliances worth mentioning that occurred in 2015 were Vertex Pharmaceuticals with the Swiss biotech CRISPR Therapeutics and Celgene with Juno Therapeutics. The former was worth US\$2.6Bn while the latter reached an up-front payment of US\$1Bn, including a 10% equity stake in the biotech to cement a deal already in place.

Unfortunately not all alliances end up in success; after all divergence of goals is inevitable since they enter an alliance in the first place to benefit from different strategic reasons. Most industries alliances have a failure rate exceeding 50%-60%¹¹⁰ due culture mismatch – whether because sharply different in size or have disparate corporate culture – many ending up even in court battles over IP rights and royalty agreements¹¹¹.

2.3.2 Licensing

Another common practice for big pharma to bolster their portfolios with innovative products is to in-license them from other companies. This strategic tool allows companies to rebuild pipelines while countering the risk of failure of high profiles products they might already develop in-house, as Merck did in the past. In-licensing therefore allows big pharma “to spend less money to cherry-pick the compounds they desire instead of having to acquire the whole organization and dealing with the (complexity) of merging the two organizations” (Cohen et al).

The other side of the coin is that companies can also decide to out-license their products to others. Denise Scots-Knight – CEO and Cofounder of Mereo BioPharma Group – states in an interview to EY how she created a startup that leveraged third party funding to in-license portfolio of diversified phase II products from pharma. These deals are structured in such a way that pharmaceutical companies’ returns are linked to the success of the products they out-license, receiving either a royalty on the sales or a share of the licensing income; other than the equity investments companies carries no product risk. “With this kind of deal structure, [pharmas] have the potential to win big via equity stakes. And since the value of that equity grows if the products are successful,

¹¹⁰ Cohen et al., *Strategic alternatives in the pharmaceutical industry*, Managerial Challenges in the Pharmaceutical, Biotech, and Medical Device Industries, Kellogg School of Management; Gueth, A. (2001). *Entering into an alliance with big pharma*. *Pharmaceutical Technology*, 25(10), 132-138.

¹¹¹ For example the dispute between Abbott Laboratories and Cambridge Antibody Technology (CAT) over the size of the royalties’ payments for Humira.

[companies] remain closely aligned with Mereo’s ambitions [...]. It’s also in [pharmas] interest if we in-license products from other biopharmas” (EY, 2016, p.59).

The downside to this approach is that it has quickly become the “*pipeline solution du jour*”¹¹² and furthermore due to the increasing licensing activity up-front payments have gone up.

2.3.3 Divestiture

Divestitures also remain a part of the strategic mix conducted by biopharma; over the past several years asset selling has accounted for about a quarter of all M&A. Let’s think to the asset swap by Sanofi and Boehringer Ingelheim worth US\$25Bn. The deal saw Sanofi’s animal health business exchanged for Boehringer’s consumer unit and cash. Also Novartis preferred to out-license US rights to three CODP treatments to Sunovion Pharma. Disposing of non-core assets and business units will continue to be a distinctive feature of today’s industry trend.

Given the current market challenges and opportunities, with increasingly high pressures from the payers, the costs and risks to develop innovative drugs will continue to surge. It is crucial, therefore for big pharma companies to pursue the most diverse strategic alternatives they deem necessary to increasing their productivity and maintain the historical high growth rates. “As business environment continues to evolve, companies must continue to implement new approaches to improve their product pipelines and look for new patients and markets to serve. While doing this they need to rigorously assess their business, ensuring their strategies are financially sound, perform strong portfolio management to target areas where they can provide novel medicines in unmet need therapeutic areas” (Baines, 2010, p.27).

¹¹² Cohen et al., *Strategic alternatives in the pharmaceutical industry*, Managerial Challenges in the Pharmaceutical, Biotech, and Medical Device Industries, Kellogg School of Management.

2.4 Portfolio Management

In finance, the role of a portfolio is to diversify risk by picking a collection of assets that lower the combined risk profile while providing good returns. Once an acceptable level of risk is identified, its construction is strategy free. In the context of corporate strategy this is not the case because the portfolio represent the means through which resources are allocated in order to deliver strategy. As David Matheson defines it, a business portfolio is “a related set of assets that compete for resources and deliver value for an organization”. The portfolio management institute (PMI)¹¹³ completes this definition by adding that the components of the portfolio may or may not be interdependent but they are managed as a group to achieve strategic objectives.

Portfolio management thus plays a critical role and it is a common business function across all industries, in particular within innovative ones. “Portfolio management creates a dynamic capability to react purposefully to changes in the market [...] and (it) is all about providing a strategic perspective and [...] ensure that resource allocations are in line with corporate strategy, by seeking balance across a range of dimensions” (Arthur D. Little, 2015, p.6). The process includes identifying, prioritizing, managing and controlling projects to achieve specific business objective and when poor portfolio decisions, not aligned with the company’s strategy, are taken these can significantly impact firms’ performance.

In the context of the pharmaceutical sector, portfolio management is defined as a set of activities that allow companies to select, develop and later commercialize a pipeline of new products aligned with the corporate strategy, in order to continue to grow profitably over the long-term¹¹⁴. Within a single pharmaceutical firm the simultaneously development of hundreds products that can cost hundreds of millions of dollars over 5-15 years and fail most of the time, the ability of portfolio management to improve decision-making can have a significant impact on the bottom line¹¹⁵. Pharmaceuticals firms have relied on portfolio management to continuously make decisions regarding their pipeline, because of the abundance of project alternatives at every level of the drug discovery and development process, but even after products are launched in the market. Indeed, the impact of rising and falling productivity levels has led pharma firms to pay closer attention to their portfolios and look for established framework and set methodologies to help them balance their portfolio and remain

¹¹³ As cited in Jones C.M., (2016), *Managing Pharmaceutical Research And Development Portfolios: An Empirical Inquiry Into Managerial Decisions Making In the Context of A Merger*, Dissertation. Georgia State University, Spring 2016.

¹¹⁴ Kester et al. (2011), *Exploring Portfolio Decision-Making Processes*. Journal of Product Innovation Management, Vol. 28(5), pp.641-661.

¹¹⁵ Smith D., *Why is Portfolio Management So Successful in the Pharmaceutical Industry?* Enrich Consulting, 2014.

competitive. Indeed as Tiggermann et al. (1998) state the most effective use of portfolio management is not the value calculation, but rather how the information generated are helpful in developing, defining and carrying out the overall business strategy.

2.4.1 Portfolio Analysis

Managing a multi-business company can be challenging; if on the one hand diversity can be a great source of competitive advantage, on the other hand it also entails fundamental difficulties because each business shows its own growth potential, operates in different competitive environment and requires singular strategic decisions to ensure the overall achievement of corporate goals¹¹⁶. One of the main activity through which corporate management creates value is by effectively managing its overall corporate portfolio, but to guarantee success organizations need to find methods for assessing the balance in their portfolio, which will help them with an optimal allocation of resources¹¹⁷.

Portfolio analysis¹¹⁸ – the process used in strategic planning to assess a company’s competitive position and business performance relative to its market in order to optimize investments and efficiently allocate resources towards the right business opportunities – therefore represents the conceptual framework that guides and assists management in corporate strategic decision-making¹¹⁹. Keegan et al. (1992) defined portfolio analysis as “a way to assess the needs, allocate resources and spread risk across the (business units or products) which contribute to the achievement of corporate objectives”. Some business units may have higher and more attractive growth and profit potential than others and may differ in terms of cash flow characteristics – some are net cash generators, others require to grow in attractive market or will be using cash in declining ones. Either ways this is

¹¹⁶ Haspeslagh, P. (1982), *Portfolio planning: Uses and limits*, Harvard Business Review 60 (1), 58-73

¹¹⁷ Hooley G.J., Saunders J.A., Piercy N.F., (1998). *Marketing Strategy and Competitive Position*, 2nd Edition, Hertfordshire, England: Prentice Hall Europe; West, Ford, Ibrahim (2010). *Strategic Marketing*. 2nd Edition, Oxford University Press.

¹¹⁸ Portfolio analysis can be discussed from the perspective of business but also from the angle of the single products in a company portfolios. In the discussion that follows this thesis the tools and models taken into consideration can be applied to both business and products are interchangeably.

¹¹⁹ Fifield, P. (1992). *Marketing Strategy*. Oxford, England: Butterworth Heinemann Ltd; Jain, S.C. (1993). *Marketing planning & strategy* (4th ed.). Cincinnati, Ohio: South-Western Publishing Co.; Aaker, D.A. (1995). *Strategic Management* (4th ed.). New York, NY: John Wiley & Sons Ltd.; Byers, L.L., Rue, L.W., & Zahru, S.A. (1996). *Strategic management*. Chicago, IL: Richard D. Irwin; Thompson, A.A., & Strickland, A.J. (1996). *Strategic management: Concepts & cases* (9th ed.). Boston, MA: Irwin McGraw Hill; Kotler, P., & Keller, K.L. (2009). *Marketing management* (12th ed.). Upper Saddle River, NJ: Pearson Prentice-Hall; Kotler, P., & Armstrong, G. (2010). *Principles of marketing* (13th ed.). Upper Saddle River, NJ: Pearson Education.

when portfolio analysis kicks in to “help diversified firms assess the balance of business¹²⁰ in its portfolio and guide resource allocation among them [...], allocating strong resources to more profitable businesses – likely its core business – and minimal or no resources into business with less or no margin” (Udo-Imeh et al., 2012, p. 104). Hence, the aim of portfolio analysis include:

1. *Analyze* the current portfolio and decide how to allocate investments.
2. *Develop* growth strategies to add new products into the portfolio to fill the gaps.
3. *Decide* which businesses or products should be divested and no longer be retained.

2.4.1.1 Tools & Models:

The basic question multi-business corporations need to answer is: “how to manage our business portfolio in order to generate as much value as possible?” Portfolio analysis tools support managers in safeguarding a balanced heterogeneous portfolio, allocating limited resources among the different products or strategic business units (SBUs) while visualizing the best growth strategies for the organization¹²¹.

Every company strives to run businesses in highly attractive industries while being strongly competitive, but managing effectively a heterogeneous variety in the portfolio can be hard. Matrices, in the context of corporate strategies, are used as visual representation to support management decision-making since they:

- Provide information on the portfolio competitive position and determining balance in terms of cash generation and growth prospects;
- Offer suggestions about strategies to pursue;
- Define priorities in terms of resource allocation among the different businesses within the portfolio on the basis of each business’s market attractiveness and competitive position.

Matrices are the most widely used form of strategic tools companies rely on to keep their business portfolio in equilibrium: they provide the necessary information to manage and maintain the portfolio balanced in terms of industry attractiveness and business competitiveness. Each matrix usually present mainly two dimensions:

1. An **internal dimension** – that considers the businesses’ competitive ability in the industry and how it will perform in the market;

¹²⁰ Hill and Jones (1989) defined a balance portfolio as one that enables a company to achieve growth and profit objectives associated with its corporate strategy without expsing the company to excessive risks.

¹²¹ Jain, S.C. (1993). *Marketing planning & strategy* (4th ed.). Cincinnati, Ohio: South-Western Publishing Co.; Kotler, P., & Keller, K.L. (2009). *Marketing management* (12th ed.). Upper Saddle River, NJ: Pearson Prentice-Hall.

2. An **external dimension** – that measures the overall degree of industry attractiveness where the business plays.

It is even possible to add a third dimension – the size of the circle's areas – that reveals the importance of each a business with respect to the others within the portfolio. The discussion that follows reviews four of the main matrices in terms of their characteristics, strategic implications and limitations.

Boston Consulting Group (BCG) Matrix – also known as the growth-share matrix – is one of the best-known approaches to portfolio analysis as well as the earliest and simplest to be developed in the mid-1960s by Bruce D. Henderson¹²². Its main objective is to identify the cash flow requirement of each business, while focusing on the *rate of market growth* and *relative market share* as proxy for the industry attractiveness and competitive position respectively, to compare the strategic positions of each business. The matrix is a 2x2 with four quadrants where the organization's portfolio is displayed on the basis of the values obtained from the calculation of the market growth rate¹²³ in the current year on the vertical axis - measuring the attractiveness of the external environment independent of the firm position – and of the relative market share¹²⁴ on the horizontal axis – as indicator of competitive strength.

Market share has been picked as the single index of competitiveness on the idea that it represents a profitability¹²⁵ indicator: the higher the market share detained by a certain business, the higher the cumulative volume of sales and the greater economies of scale to count on. Aaker (1995) supports this view and further claims that highest-share companies likely enjoy size advantages in terms of brand recognition and strongest bargaining power. Furthermore they may best positioned to exploit their position along the learning curve resulting in lower unit cost due to reduced learning effects. Business market share per se is not a strong indicator since there is no benchmark to compare it to; for this reason they have chosen a relative market share in which the business' market share is analyzed with respect to the one belonging to the main competitor. Conventionally a common indicator – either 1 or 1.5 – is established as a reference point in order to define whether the company's business market share is higher or lower with respect to its main competitor and consequently if it is in a good competitive position or not. Also in the case of the market growth rate a benchmark is defined, which usually depend on the industry in which the different businesses within the organization's portfolio compete: if

¹²² Hofer, C., & Schendel, D. (1994). *Portfolio analysis*. In B.D. Witt & R. Meger (Eds.), *Strategy: Process, content, context* (pp.182-185). St. Paul, MN: West-publishing Company

¹²³ Market growth rate = $\frac{\text{total market } (x) - \text{total market } (x-1)}{\text{total market } (x-1)} * 100\%$

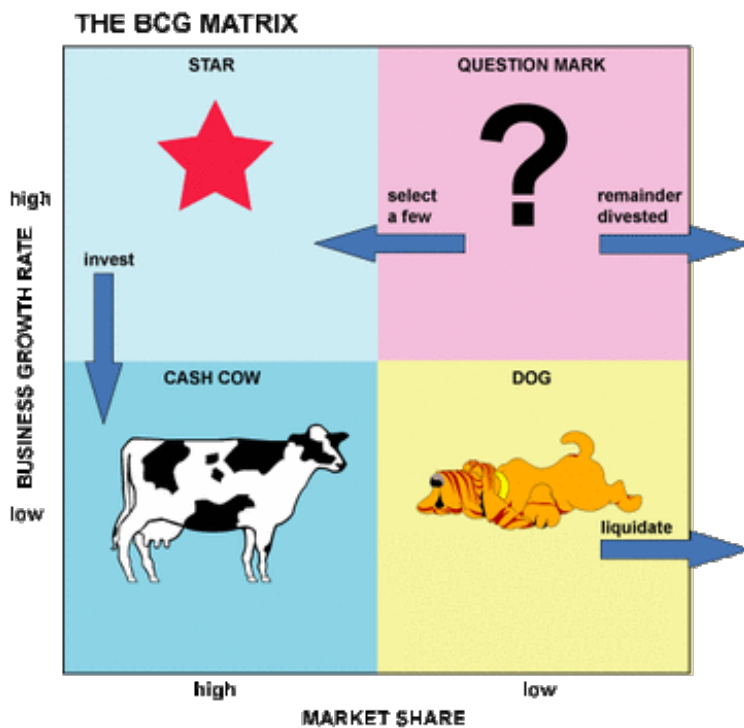
¹²⁴ Relative market share = $\frac{\text{Sales (target business)}}{\text{Sales (leading competitor)}}$

¹²⁵ In the literature many empirical studies have confirmed this correlation such as Aaker (1995), Hooley et al. (1998) and Hax and Majluf (1990) just to cite some.

the firm follows a correlated diversification strategy for its businesses then the industry average growth rate is used as benchmark, otherwise the mid-point reference is set at growth rate for the economy (GDP) for diversified companies playing in just one country or the growth rate of the business in case of unrelated and geographically diversified company. Moreover as Vernon (1966) suggested, market growth is directly linked to the business life cycle; an industry indeed is attractive when it is in expansion or in the development phase because competition is not fierce and a firm can implement more aggressive penetration strategies, on the contrary they become less attractive when the business moves to the maturity or declining stage.

Putting the two dimensions together, each quadrant of the matrix exhibits a different pattern of profit and cash flows, offering distinctive strategic choices to adopt (Figure 37).

Figure 37 The BCG Matrix



Cash Cows have high market share in slow-growing industries, thus holding a competitive position in mature markets that comes from being further down the experience curve¹²⁶. The business units positioned in this quadrant generate cash in excess of the amount needed to maintain them alive and hence they show higher profit margins¹²⁷. Even though they are settled businesses in mature markets, corporations value their ownership due to their cash generating qualities. In fact, their strategic objective is to hold sales stable - they are “milked”

¹²⁶ Hill, C.W.L., & Jones, G.R. (1989). *Strategic management: An integrated approach*. Boston, MA: Houghton Mifflin Company

¹²⁷ Kotler, P., & Keller, K.L. (2009). *Marketing management (12th ed.)*. Upper Saddle River, NJ: Pearson Prentice-Hall

continuously with little investment, to pay the company's bills and support other businesses that need investments. *Dogs* on the other hand have low market share in mature markets. These businesses typically breakeven, generating barely enough cash to maintain the business's market share constant. Plausible reasons are to be found on a slow progression along the learning curve mainly because of cost disadvantages and low long-term potentials. According to Agbonifoh et al. (2007) strategies to follow are either: niching – targeting unique positions in the market in which it has specialized competencies and capabilities that will help it dominate the market or harvesting – drastically reduce all costs associated to the business unit to optimize the available cash flows or divesting – sell the business as a going concern. Indeed, deciding which business to sell is vital to a company's long-term value creation as much as deciding which business to keep or acquire. As Ruth Da Backer once said in a McKinsey interview¹²⁸ “the ‘best’ owner of a business is whoever can generate the highest value from it. [...] Explor(ing) the best-owner mind-set can help companies overcome barriers to profitable divesting (because) even if a parent company's distinctive capabilities stay the same, a business's needs change as it matures and competitive landscape evolves”. *Question Mark* – also called the problem child, represents all the businesses that operate with a low market share in a high growth market. They are usually the starting point for many businesses since they may have the potential to gain market share, become market leaders and eventually cash cows when the market matures. They generally require considerable investment to keep up with market development, absorbing large amount of cash with the risk that they may not succeed in becoming market leaders degenerating into dogs. Hence these businesses are labeled as question marks due to the uncertainty management faces in deciding whether they are worth investing or withdraw them from the market. *Stars* - these are businesses with high market share in fast-growing industries. They are market leaders and as such they generate considerable income, but at the same they require substantial funding to fight off competition and sustain growth¹²⁹. Thompson and Strickland (1996) also pointed out that funds are needed to expand production facilities and meet working capital requirements. As the industry matures and growth rate slow down stars can either become the next cash cows or dogs; in order to become tomorrow's breadwinners¹³⁰ firms must both protect their existing market share as well as acquire proportion of the existing market to maintain their leadership position.

¹²⁸ Mckinsey&Co., *Strategic portfolio management: Divesting with a purpose*, Strategy & Corporate Finance, October 2016.

¹²⁹ Agbonifoh, B.A., Ogwo, O.E., Nnolim, D.A., & Nkemnebe, A.D. (2007). *Marketing in Nigeria: Concepts, principles & decisions* (2nd ed.). Aba, Nigeria: Afritowers Ltd

¹³⁰ as cited in Hooley et al. (1996)

As shared by Hill and Jones (1989) the objective of the BCG model is to identify how corporate cash resources can be employed to maximize growth and profitability. Therefore to ensure an optimal resource allocation and a balanced portfolio, the following recommendations are outlined¹³¹:

1. Use the cash surplus from any cash cows to support the development of selected question marks and nurturing them into becoming stars. The long-term objective of the company is to consolidate the position of stars thus making the portfolio more attractive.
2. Question marks with uncertain long-term prospects are divested in order to free up resources.
3. Divesting any dog.
4. In the case companies were lacking sufficient cash cows or question marks it should consider external growth strategies such as acquisitions in order to build a more balanced portfolio to ensure growth and positive profit outlook for the future.

As stated by BCG in the 1970: “only a diversified company with a balanced portfolio can use its strengths to truly capitalize on its growth opportunities. The balance portfolio has: stars whose high share and high growth assures the future; cash cows that supply funds for that future growth; and question marks to be converted into stars with added funds”.

Simplicity is both its effectiveness as well as the limitation of this tool. Even though it offers a clear graphical display of a company’s portfolio and analysis can be adaptable from products to business units, it is too simplistic and can only be useful as a preliminary view before diving into more detailed and rigorous analysis. Furthermore, the model shows problems of market definition and an even greater problem is the implicit assumption that every business in the portfolio is independent – a contradiction to the very reason why multi-business corporation exists: the synergies among the businesses¹³².

The General Electric/ McKinsey (GE) Matrix was one of the many variants of the BCG model that followed in the 1970s developed by the well-known management consultancy firm and General Electric in the USA. Indeed this model was inspired by the need to develop a portfolio-planning tool to evaluate GE’s plans for its different businesses in order to fund only the ones with the greatest success potential¹³³. The GE matrix is still a two-dimensional grid but unlike the BCG matrix it uses multiple indicators to determine a business’s strengths as

¹³¹ Hill, C.W.L., & Jones, G.R. (1989). *Strategic management: An integrated approach*. Boston, MA: Houghton Mifflin Company

¹³² Grant M.M., *Contemporary Strategy Analysis*, Ch. 17, pp. 433-434.

¹³³ Byers, L.L., Rue, L.W., & Zahru, S.A. (1996). *Strategic management*. Chicago, IL: Richard D. Irwin

well the market attractiveness; nonetheless even this model has been criticized for its subjective nature and the lack of standardized variables¹³⁴.

Business units are plotted against the same two dimensions of internal and external environment – namely the industry attractiveness on the vertical axis and competitive position on the horizontal one. A set of different external factors – relevant and appropriate for the industry in consideration – are assessed in order to identify the industry attractiveness, rated and then multiplied by an assigned weight according to the importance of the particular criteria. The total score is taken as reference for the industry attractiveness and then plotted on the grid. The business competitive position is obtained following the same logic, only changing the reference critical factors to reflect the internal environment. The tables below (Table 1) identify some of the most common critical external and internal success factors, as identified by Hax and Majluf (1990). Therefore, the match between the industry attractiveness degree and the evaluation of the business competitive ability makes possible to collocate businesses in one of the nine quadrants of the 3x3 matrix, on the basis of the score of the multi-factors model.

Table 1 External and Internal Critical Factors

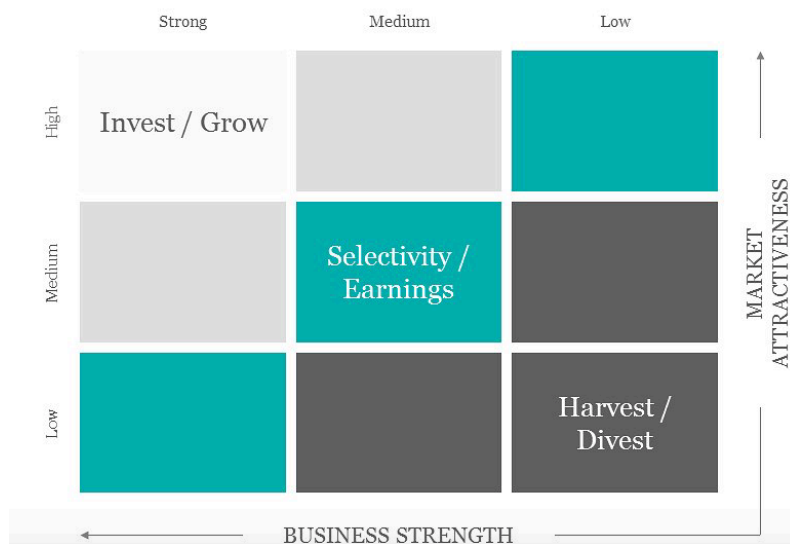
Attractiveness criterion	Weight	Rating	Weighted score
Size	.15	4	.60
Growth	.12	3	.36
Pricing	.05	3	.15
Market diversity	.05	2	.10
Competitive structure	.05	3	.17
Industry profitability	.20	3	.60
Technical role	.05	4	.20
Inflation vulnerability	.05	2	.10
Cyclicity	.05	2	.10
Customer financial	.10	5	.50
Energy impact	.08	4	.53
Social	GO	4	-
Environmental	GO	4	-
Legal	GO	4	-
Human	.05	4	20
	1.00		3.38

Source: Udo-Imeh, 2012

Critical success factor	Weight	Rating	Weighted score
Market share	10	5	.50
SBU growth rate	X	3	-
Breadth of product line	.05	4	.20
Sales distribution effectiveness	.20	4	.80
Proprietary and key account advantages	X	3	-
Price competitiveness	X	4	-
Advertising and promotion effectiveness	.05	4	.20
Facilities and location and newness	.05	5	.25
Capacity and productivity	X	3	-
Experience curve effects	.15	4	.60
Raw materials costs	.05	4	.20
Value added	X	4	-
Relative product quality	.15	4	.60
R&D advantages/position	.05	4	.20
Cash throw-off	.10	5	.50
Caliber of personnel	X	4	-
General image	.05	5	.25
	1.00		4.30

¹³⁴ Hill, C.W.L., & Jones, G.R. (1989). *Strategic management: An integrated approach*. Boston, MA: Houghton Mifflin Company; Aaker (1995).

Figure 38 McKinsey/ EY Matrix



Furthermore the circles representing the business can be added as a further dimension, informative on the business: circle's size can be either proportional to the business' sales or to the industry's dimension, with pie slices within the circle to respectively indicate either the single business contribution to total sales or the business market share¹³⁵ (Figure 38). Depending in which of the nine quadrants the business falls, different strategies for each specific business care be formulated and these can be: *invest to grow* – they attract investment because are expected to yield high returns in the future; *selectivity to grow* – these business units hold ambiguity and they are usually invested only if companies have left funds after having invested in grow businesses; *harvest* – business units performing poorly in unattractive industries. The McKinsey matrix has two main strategic implications: the former is the **allocation of investment priority** to the different company's business; in fact priority goes to businesses in the “invest to grow” quadrant, then two the ones in “selectivity to grow”, finally to the other where either invest or abandon must be decided. In the specifics, “the SBUs in three cells at the top left corner of the matrix labeled 1,2 and 4, where long-term industry attractiveness and business position are strong are given top investment priority. The strategic prescription for business units in these three cells is ‘grow and build’, with cell 1 receiving the most investment. SBUs in the diagonal cells tagged 3,5 and 7 receive steady investments to maintain and protect their positions. SBUs in the lower corner of the matrix labeled 6, 9 and 8 are candidates for harvesting and divestment” (Udo-Imeh et al., 2012, p.109) (Figure 39).

¹³⁵ Thompson, A.A., & Strickland, A.J. (1996). *Strategic management: Concepts & cases* (9th ed.). Boston, MA: Irwin McGraw Hill

Figure 39 Prescribed Strategy for Investment Prioritization according to the McKinsey/ GE Matrix

		Competitive position		
		Strong	Medium	Weak
Industry attractiveness	High	Protect position (1) <ul style="list-style-type: none"> Invest to grow at Maximum digestible rate Concentrate effort on maintaining strength 	Invest to build (2) <ul style="list-style-type: none"> Challenge for Leadership Build selectively on strengths Reinforce vulnerable areas 	Build selectively (3) <ul style="list-style-type: none"> Specialize around limited strengths Seek ways to overcome weaknesses Withdraw if indications of sustainable growth are lacking
	Medium	Build selectively (4) <ul style="list-style-type: none"> Invest heavily in most Attractive segments Build up ability to counter Competition Emphasize profit-ability by raising productivity 	Selectivity/manage for growth (5) <ul style="list-style-type: none"> Protect existing program Concentrate investments Segments where profit-ability is good and risk is relatively low 	Limited expansion (6) or harvest <ul style="list-style-type: none"> Look for ways to expand without high risk; otherwise, minimize investment and rationalize investment
	Low	Protect and refocus (7) <ul style="list-style-type: none"> Manage for current earning Concentrate on attractive strengths Defend strengths 	Manage for earning (8) <ul style="list-style-type: none"> Protect position in Most profitable segments Upgrade product line Minimize investment 	Divest (9) <ul style="list-style-type: none"> Sell at time that will maximize cash value Cut fixed cost and Avoid investment meanwhile

Source: Udo-Imeh et al. , 2012

The latter is the indication of **guidelines in the resource allocation process**. In fact, the matrix can be used to understand whether the if the investments done in the past have been coherent by testing the consistency between resources’ allocations plans and investment priorities. A comparison of the expenses’ levels on a three-years period relative to any most important business activity, e.g. marketing in the pharma sector, and their classification in one of the following: aggressive; moderate; of maintenance; of surviving. By doing so, if businesses are found outside the coherent line it means there is something to change in the allocation of resources: either it has been invested too much in less favorable business or it has been invested too less in the promising ones.

Even though the McKinsey matrix was born as a criticism to the BCG model, it had its own demerits. Indeed, the model was criticized for its subjective nature in the selection and weighting of both internal and external

factors as well as the lack of a standardized list of critical factors to be used, which creates inconsistencies and ambiguity in the classification of business units¹³⁶.

Shell Directional Policy Matrix (DPM) represents a further improvement of the BCG matrix. It measures the company’s competitive capabilities on the y-axis and prospects for sector profitability on the x-axis. The model aims at systematically analyzing the qualitative factors that impact strategic planning, comparing business sector and company position in a way that is independent from the financial forecasts¹³⁷.

The matrix uses two dimensions: the business competitive capabilities (BCC) and the industry prospective probability (IPP) – both are categorized as high, medium and low; The matrix is therefore, similarly to the McKinsey one, a 3x3 matrix with 9 quadrants (Figure 40). The main parameters considered in estimating the industry profitability prospect level include: market growth rate, market quality, environmental features and the industry situation. On the other hand the evaluation of the SBUs competitive capabilities considers factors such as market share, R&D investments and production capabilities.

Figure 40 Shell Directional Matrix

		Company competitive strength		
		Attractive	Average	Weak
Prospect for Sector Profitability	Attractive	Divest	Phased withdrawal	Double or Quit
	Average	Phased Withdrawal	Custodial Growth	Try Harder
	Unattractive	Cash Generation	Growth Leader	Leader

Source: Udo-Imeh, 2012.

¹³⁶ Hill, C.W.L., & Jones, G.R. (1989). *Strategic management: An integrated approach*. Boston, MA: Houghton Mifflin Company; Aaker (1995); Hax, A.C., & Majluf, N.S. (1990a). *The use of the Growth-Share Matrix in strategic planning*. In R. G. Dyson (Ed.), *Strategic planning: Models and analytical techniques* (pp.51–71). Chichester, England: John Wiley & Sons ; Aaker, D.A. (1995). *Strategic Management* (4th ed.). New York, NY: John Wiley & Sons Ltd.

¹³⁷ Udo-Imeh et al. (2012)

The positioning in one of the specific quadrant of the matrix implies for each specific business unit different strategic implications. Unlike the BCG matrix, which gives the management a tool to balance business opportunities among growth and mature market, the Shell matrix specifies that the majority of the businesses should concentrate around the “Leader” domain. The strategies for each quadrant, as summarized by Bank (2011), are the followings:

- **Leader** – major resources shall be focused on the SBUs in this quadrant, with the aim of maintaining this position.
- **Try Harder** – could be vulnerable over a longer period of time, but fine for now.
- **Double or Quit** – SBUs with the best prospects for the future should be invested in while the rest should be abandoned.
- **Growth** – investments should be made to allow the business to grow with the market. These businesses will generally generate enough cash to self-financing and should not depend on other corporate cash resources.
- **Custodial Growth** – Just like cash cows, these businesses should be milked without committing any resources.
- **Cash Generator** – typically these businesses are at the end of their lifecycle and are milked for cash for other areas.
- **Phased withdrawal** – move cash to SBUs with greater potential.
- **Divest** – liquidate the business and move the assets because these businesses are only draining resources to other potential units.

Even though the Shell matrix may resemble the McKinsey because of similar features, the main difference lies in the variables used to determine a business position within the matrix: the former uses more simple variable while the latter more aggregate ones. Moreover, the fact that it was developed to fit the petrochemical industries, many have pointed out the complexity in applying the tool outside this industry and assuming that the same set of criteria could be universally applicable. Furthermore, the model is of qualitative nature overall, coordinates are not the result of quantitative weighted averages.

Arthur D. Little Matrix was developed in the late ‘70s by the famous management consultancy firm that carries the same name. It was of the first portfolio management model to include the business life cycle as one its dimension. The matrix is structured as a 6x4 matrix based on two performance indicators: the *business life cycle phase* – as an indicator for the external environment – and the *business competitive positioning*. The industry life cycle phase can be classified as either: embryonic, growth, maturity or decline. Factors taken into account to determine in which phase the business falls are for example market growth rate, market share stability,

competitors amount and ease to entry. While a business position can be categorized as one of these competitive positions: dominant, strong, favorable, tenable, weak, untenable¹³⁸.

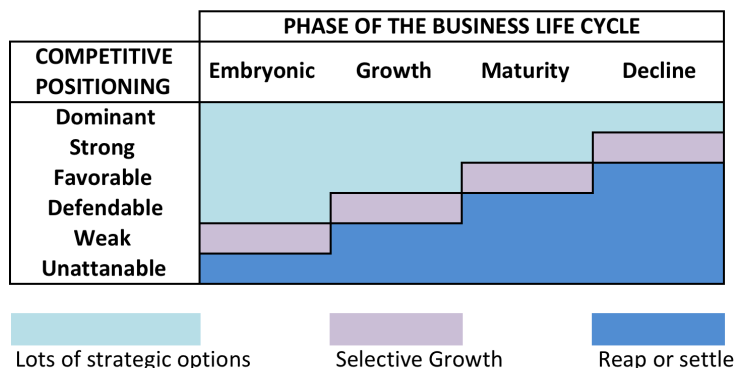
- **Dominant:** a rare position, in many cases attributable to an almost-monopoly or a protected technological leadership. This implies that the company is able to exercise influence on the behavior of others in the industry.
- **Strong:** the firm has freedom over its strategic choices without being threatened by rivals.
- **Favorable:** this position occurs when the industry is fragmented and no competitor stands out as the market leader. Firms in a favorable market position can exploit particular strategies to increase their market share.
- **Tenable:** although firms within this category are justified to staying in the industry by performing satisfactory, they are usually vulnerable to increased competition from stronger and more proactive firms in the market. Opportunities to strengthen for firms in this category are lower and profitability is best achieved as well as sustained through a degree of specialization in a small niche.
- **Weak:** Performance of companies in this position is far from satisfactory, although opportunities from improvements do exist. Unless the firm changes, it will likely be forced out the market or exit on its own.
- **Untenable:** Impossibility to go on with the business. The firm must leave the market because there is no potential to reap profits.

The assessment and further classification of the business in one particular category is done considering supply, production, commercialization and financial factors¹³⁹. “Performance indicators represented by market competitive position are valued by reference to competition, using qualitative and quantitative variables, which make up a set of determinant success factors. [...] the competitive position are weighted and scored and this results in several competitive positions according to company forces in relation to competitors on a given market, (however) these factors change over time, (and) business gain or lose ground in terms of competitive advantage, and eventually they will identify with one of the five competitive positions” (Tudor and Valeriu, 2011, p.).

¹³⁸ Mason, M. (2010). *ADL matrix by Arthur D. Little*. All about economies on the web; Udo-Imeh P.T., Edet W.E., Anani R.B., *Portfolio Analysis Models: A Review*. Journal of Business and Management, Vol. 4(18), pp. 101-120, 2012.

¹³⁹ Tudor, I. F., & Valeriu, C.C. (2011). *Product portfolio analysis: Arthur D. Little matrix*.

Figure 41 Arthur D. Little Matrix



Source: Elaborated from Prof. Brunetta Slide material

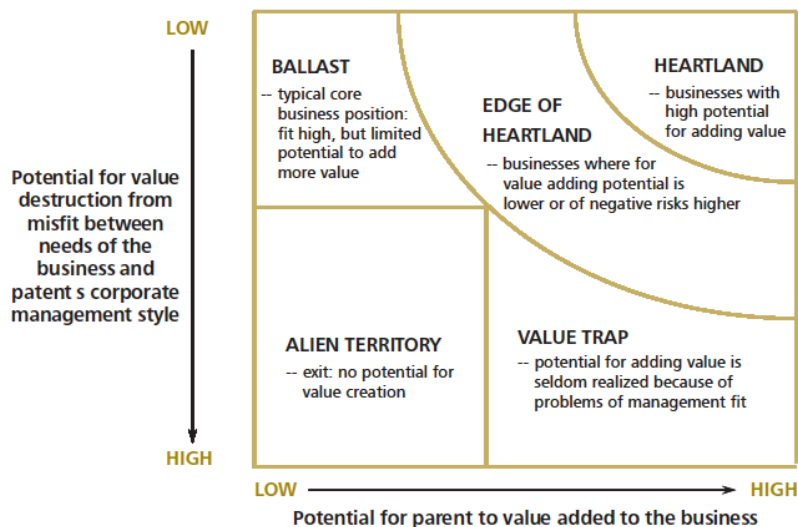
The strategic suggestions that come out from this matrix are mainly three: reap or settle, selective growth or lots of strategic options (Figure 41). If the business falls in the dark blue area then it must harvested or abandon – this is usually the case for companies with untenable or weak position and not in an embryonic phase, in a tenable position but in a mature or declining phase and even in a favorable position but in a declining phase. If the business falls on the diagonal the matrix suggest selective growth, which means to invest in the business only if can be forecasted that by increasing the competitive position the business can shift in the upper part of the matrix. The light blue area of the matrix represents an ocean of strategic possibilities to undertake. The businesses within this part are worth keeping and investing in and trying to move them forward along the competitive positions. Each one has, nevertheless, a variety of strategic choices – from internal to external growth or alliances – it can implement to remain in the market and improve its competitive position.

Also this matrix has been criticized for being too qualitative in nature, especially when assessing the business critical factors to identify its competitive position since they may give rise to biases in judgment and the model’s downsides include the difficulty in objectively evaluating variables.

When matrices, as portfolio analysis tools, first came out in the ‘60s everyone was caught in the romance with the logic of these strategic tools. Only throughout the years the enthusiasm turned to criticism; however it is important to point out how no matrix is superior to the others, each one has its own advantages and downsides and each one can be used depending on the need of the company and the industry in which it operates. Bianchi and Sedehi (1995) criticized traditional portfolio models of being normative instead of descriptive; partial instead of systematic; static instead of dynamic; deterministic, instead of stochastic and for referring only to some variables instead of being well-balanced among both in terms of key variables and drivers through which it is possible to affect product portfolio performance.

The criticisms and limitations of the traditional portfolio matrices led the development of newer variants that though theoretically sounder do not appear to be so popular among marketing and management practitioners. Udo-Imeh et al. (2012) list some of latest models such as the SPACE Matrix, the strategic triangle of 3 C's and the ME/CP strategic framework. Micheal M. Grant in its seventh edition of *Contemporary Strategy Analysis* also mentions the Ashridge Portfolio Display, based upon the work of Goold, Campell and Alexander's parenting advantage framework, which assumes that the value creating potential of a business within a multi-business company's portfolio depends not just upon the characteristics of the business but also the characteristics of the parent company. The focus is therefore on the fit between a business and its parent company (Figure 42); indeed "creating value from the configuration and reconfiguration of a portfolio of business involves complex issues of fit (between the business and the parent) that requires insight into the fundamental strategic characteristics of the businesses and the nature of corporate management systems and style" (Grant, 2010, p.434). In the matrix the horizontal axis shows the potential for a parent company to add value within the business by for example applying corporate-level management capabilities to the business, sharing resources and capabilities with other business or even reducing transaction costs. On the vertical axis, instead, is measured the potential for value destruction by the parent company, which usually result because of a mismatch between the business needs and the management's ones, incompatibility with the management mindset or inappropriate strategic guidance.

Figure 42 Ashridge Portfolio Display



Source: M. M. Grant, 2010

Portfolio analysis, whether performed at the business or product level, is a valuable instrument that gives the top management an overview on the short-to-medium term prospects of the various businesses, and supports

them in deciding whether the portfolio is adequate from the perspective of corporate growth, profitability and strategic fit to company's long term goals¹⁴⁰. Even though these tools do not provide clear-cut strategic recommendations, they do facilitate the strategic planning process leading to strategies improvements, by summarizing information on the overall company's market position and giving insights on the balance of the businesses, their relative strengths to competition as well as the opportunities open to them¹⁴¹. Exercises of portfolio analysis are not performed to dictate any strategic decisions but they do provide corporate management with the data needed to make informed decisions. Nevertheless their greatest challenge is the implementation at the organizational and operational level because they continue to remain "well-known but underutilized and misunderstood planning tools" (McDonald, 1990, p.11).

2.4.2 R&D Portfolio Management

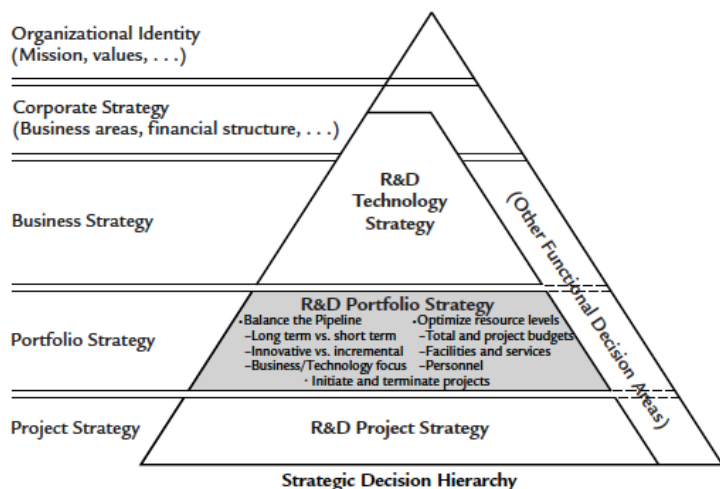
Conceptually R&D portfolio management falls within the more general area of portfolio management with the same objectives: reviewing the allocation of corporate resources and ensuring that the combination of its project-level activities will allow meeting its strategic objectives. Indeed, portfolio decisions begin first and foremost at the R&D level by balancing the potential delivery of R&D results over time, determining which R&D projects should be funded and at what level. R&D portfolio strategy, therefore, reconciles the business strategy with the single R&D projects strategies by balancing the existing projects and new opportunities as well as optimizing the resources within the pharma pipelines (Figure 43). Thus, the goal of (R&D) portfolio management is not to pick which projects are the best but to pick the best set of projects to achieve firm's goals.

According to Bode-Greuel and Nickisch (2008) R&D project management is the operative instrument for the execution of portfolio decisions. Indeed projects are the first level of analysis; they are later selected not only on the basis of their characteristics but also according to their fit within the existing portfolio in terms of risk-reward and the firm resource availability: each projects within the pipeline optimizes the value per investment at comfortable level of risk set by the firm itself (Figure 44).

¹⁴⁰ Hooley, G.J., Saunders, J.A., & Piercy, N.F. (1998). *Marketing strategy and competitive position* (2nd ed.) Hertfordshire, England: Prentice Hall Europe

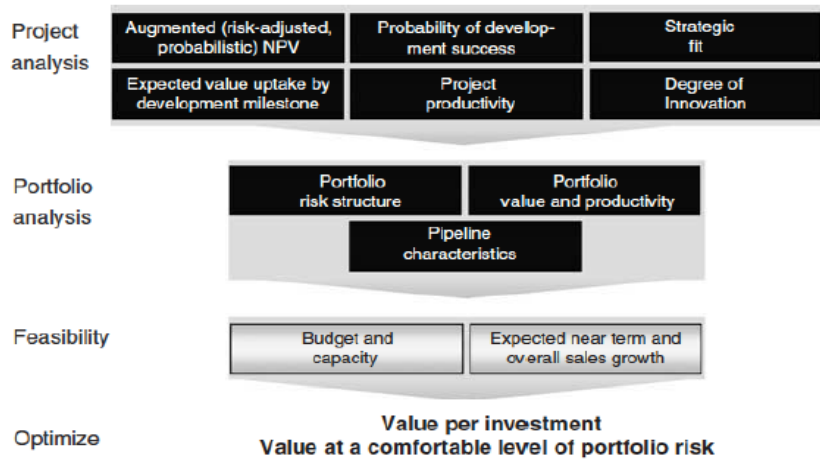
¹⁴¹ Aaker, D.A. (1995). *Strategic Management* (4th ed.). New York, NY: John Wiley & Sons Ltd; Doyle, P., & Stern, P. (2006). *Marketing management and strategy* (4th ed.). Essex, England: Pearson Education Ltd.

Figure 43 The Role of R&D Portfolio Strategy



Source: Matheson & Matheson, 1997

Figure 44 Portfolio Management Funnel



Source: Jones, 2016

Just as a pharmaceutical company’s portfolio should balance between new launches and more mature products, so its R&D pipeline must strike a similar balance between innovative but risky projects and incremental ones with more certain results. Operational business managers are tempted by incremental projects with greater certainty and more immediate returns, especially when corporate culture punishes failure and applies incredibly high discount rates. Ironically, despite managers look more confidently in the direction of incrementalism they still expect to discover the next company’s blockbusters and this may explain why instead of focusing on

innovative R&D, firms' laboratories quickly become servant of short-term business needs with the result that real innovation must be sought through acquisitions¹⁴².

Key for pharmaceutical companies is determining the critical mass in their portfolio of discovery, development and marketed products in order to deliver sustainable future value. As such the discovery pipeline must be considerably large to keep the development pipeline filled, to account for the attrition and failure probabilities along the discovery pathway. Firms that engage in R&D face the critical task of selecting projects that will eventually, if they make it to the market, contribute to both to the short and long-term corporate profitability. The process for portfolio selection at the R&D level becomes more challenging due to the inability to predict outcomes and estimate the commercial value of the project. In fact, when dealing with R&D projects, companies must consider:

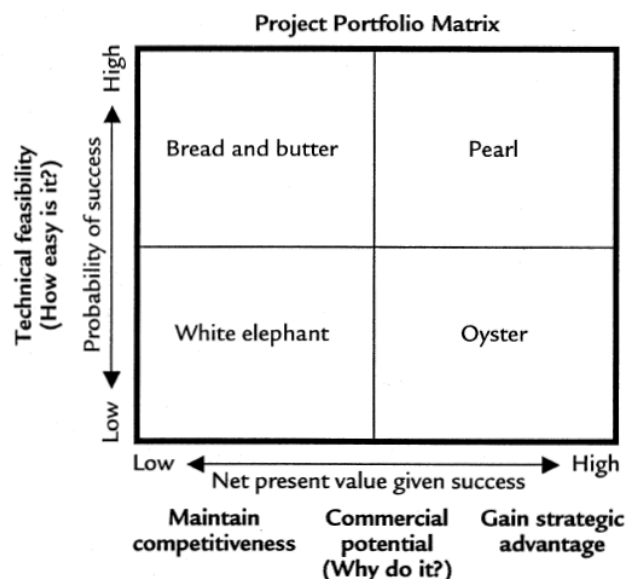
- The long-term versus the short-term balance of risks and strategic business needs;
- The hurdles to overcome in order to achieve success and creating a commercially viable product;
- The value of the commercial success, most commonly estimated through the risk-adjusted Net present value (r-NPV).

Unfortunately resources are often limited for every company in every sector and a major challenge in portfolio management is “saying no to a good idea to fund a better one and making decisions about project selection [...] prioritization and allocation of resources based on a well-balanced portfolio” (Creswell, Dec. 2011, p.1). For this reason Matheson & Matheson (1997) first introduced the so-called *R&D Grid: Project Portfolio Matrix*¹⁴³ aimed at helping companies to understand projects differences and their contributions to the overall portfolio. The grid measures therefore projects in terms of technical difficulties and commercial potential, classifying them in bread and butter, pearls, oysters and white elephant according to each project characteristics (Figure 45).

¹⁴² Matheson D., Matheson J. *The Smart Organization: Creating value through strategic R&D*, 1997, Ch. 10, pp.199-220.

¹⁴³ see note 120.

Figure 45 R&D Grid: Project Portfolio Matrix



Source: Matheson & Matheson, 1997

The vertical axis reflects a project success probability in overcoming all hurdles, while the horizontal axis measures the potential commercial value through the expected net present value of cash flows (eNPV). Simply put, projects on the left hand of the x-axis maintain competitiveness in existing businesses, while those on the right hand create new strategic advantages by means of incremental or radical innovation. In the specifics, bread-and-butter projects are projects with high probabilities of success but a moderate commercial value since they are usually improvements in existing products. A company needs these types of projects to fulfill the need to produce regular cash flows for existing SBUs and to support the short-term profit objectives. Pearls, on the other hand, show the greatest potential both in term of technical and commercial success. They represent radical innovations – typically in pharma sector pearls would be phase III drug for highly unmet clinical need.

In an ideal world companies would hold dozen of pearls in their R&D pipelines, but in reality pearls are rare and are found only after opening many oysters. Oysters are early stage products that have blockbuster potential but initially very low probability of success, the majority are expected to fail but those that will succeed have the potential to win big. As over time the uncertainties surrounding oysters disappear they will shift to the other quadrants. Projects in the lower left corner are defined as the king’s white elephants¹⁴⁴: they consume resources with low probability of success and commercial value. No company would select those projects on purpose to be

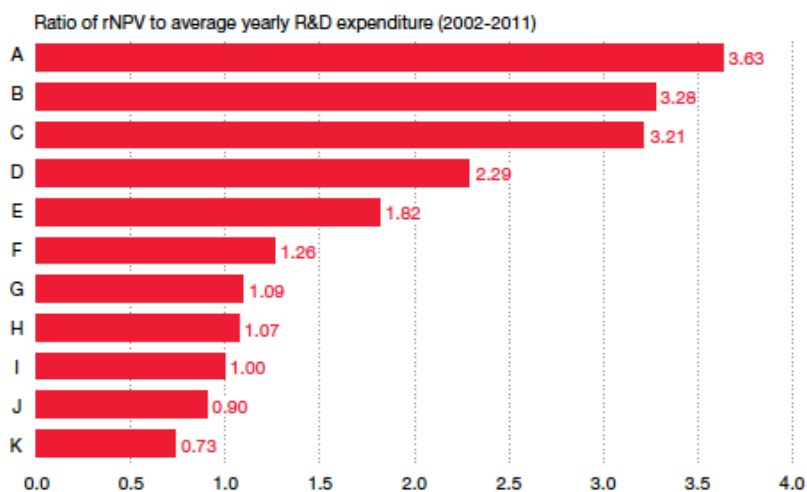
¹⁴⁴ Matheson (1997) explains the legend behind the white elephants. According to the legend in fact, the king of Siam distributed white elephants to his troublesome underlords. The rare animals were considered sacred and required lavish care and feeding, and could not be required to work. In this way, the animals consumed their lords’ resources, reducing the possibility of creating mischief in the kingdom.

part of their portfolio, but as a matter of fact almost every company own them. They may have started as oysters or bread-and-butter projects and then moved across the grid to white elephants as defects started to emerge. It is imperative for a company with a healthy portfolio to admit, if present, the existence of white elephant projects and subsequently put in place a process to discard them.

Matheson explains that the grid should help companies to assign to each R&D project an appropriate quadrant based on a quantitative evaluation of its opportunities. Companies should capitalize on pearls, eliminate or reposition white elephant, balance resources between bread and butter and oysters projects to achieve an overall alignment with the corporate strategy. Although projects are defined quantitatively, they are each qualitatively different one another: bread and butter are incremental products or process innovations to generate short-term results; pearls are valuable projects that have the potential to become breakthroughs to be exploited; oysters are defined by uncertainty and it should be quickly determined which oysters contain pearls and which are empty so to avoid spending time on failure. In this context, capitalizing on pearls and discarding white elephant projects represent the easy portfolio decisions, the difficult ones concern funding on bread-and-butter and oyster projects; it is by making these difficult choices, between long-term and short-term, that management defines corporate value creation: “business pressures tend to favor bread-and-butter projects. It is rare that a manager has lost his job by supporting incremental R&D for established products – politically safe thing to do. But incremental R&D does not sustain competitiveness over time, (it is) the groundbreaking work associated with oyster project [...] needed to renew the business in the long run” (Mathenson & Mathenson, 1997, p.207)

Companies R&D portfolios however should not only be commented and analyzed in isolation, corporate management needs to consider how strong or weak from a competitive perspective the company’s portfolio is relative to those of other competitors in the sector. A Pwc (2012) analysis shows the significant differences in the quantity and quality of the key candidates in phase II and phase III within the pipelines of the 11 industry major companies on the basis of the relationship of risk-adjusted NPV and the average yearly R&D expenditures (Figure 46). What accounts for the differences for the companies is the distribution of value among the different pipelines driven mainly by two factors: the therapeutic focus and the ability to risk management. Deep diving into the promising pipelines of the first three companies that shows the highest values in terms of rNPV, it can be observed that they “have decided on the rules by which they’re playing and stuck to them. That’s what (...) all pharma companies should do: weed out their weakest compounds, with disciplined and continuous portfolio management; concentrate on the frontrunners, with some bread-and-butter molecules to provide stability and few long shots that might generate really high returns” (Pwc, 2012, p.37).

Figure 46 r-NPV to R&D Expenditure Ratio for 11 Major Pharma Companies (Pwc analysis)



Source: Pwc, 2012.

2.4.2.1 Financial Valuation Metrics

The competitive environment in today’s biopharmaceutical marketplace is forcing organizations to be more flexible, responsive and efficient than ever before. Their main challenge is to ensure that their project portfolio remains aligned to their strategic goals, making sure that the most valuable projects are selected, prioritized and receive the appropriate resources, whether internally or externally sourced. The pressure on companies to replenish pipelines with innovative drugs that have high potential for approval and reimbursement has driven companies to revise their portfolio strategy over the last decade, allocating R&D budget to projects that maximize the total value of the entire portfolio relying mainly on financial metrics and focusing on individual products’ revenues and costs¹⁴⁵.

As it is commonly acknowledged the pharma sector invests more in R&D than any other sector and pharmaceutical projects have an extremely high-risk profile, expensive and last for long time frames. Given these statistics and the unpredictability of the pipeline outcome, managers are driven to make educated guesses on the basis of past experiences of prior success and failures. In order to avoid the consequences of bad outcomes they tend to rely, sometimes even over rely, on standardized financial metrics and criteria that have the potential to pick winners and predict which projects can achieve the higher level of return on investment. As R&D projects selection becomes more challenging, solid financial valuation metrics come into play rather than

¹⁴⁵ Quintiles, *Strategic Portfolio Management & New Influencers in R&D Decision-Making*, White Paper, 2013.

relying only simply qualitative methods, as in the case of the consultancy firms' matrices outlines above, and strategic decisions are based upon those valuations.

Portfolio selection is the most critical aspect of portfolio management; in fact, “drug target and candidate selection are two key decision points within the drug discovery process, and all firms use certain selection criteria for decisions on which targets to accept into their discovery pipelines and which compounds will proceed to the development stage” (Jekunen, 2014, p.2012). This stage is characterized by uncertainty and continuous discovery of new information, nevertheless demanding important strategic considerations: selection must consider that competition among drug candidates for limited resources can take place and that the average project development times must not be too long in order to avoid late commercialization. Selecting from a pool of available competing projects can thus represent a difficult decision and multiple projects dimensions have to be considered: first and foremost how the addition or removal of the single project impacts the overall portfolio. This confirms the foundation that a robust R&D portfolio management methodology must be in place to carefully balance the specific R&D project expected value with its expected impact in terms of technical and commercial uncertainties. For this reason firms tend to rely heavily on quantitative modeling methods which present selection decisions as rational evidence-based¹⁴⁶; In fact, according to Smith and Sonnenblick (2013) the success of portfolio management lingers on having a strong portfolio group with access to projects data and their ability to manipulate those data in to concrete what-if questions. Generally the evaluation of those projects that successfully ace phase II clinical trials and obtain proof of concept is grounded on quantitative financial parameters before entering full development. However, firms that rely solely on financial methods for project selection and decision-making perform worse than the other firms according to Kester et al. (2011).

The ideal structure of a pipeline is driven by the drugs' development costs, the likelihood of successfully overcoming all clinical trials and being approved on the market as well as the final expected profitability. Given this setting the development of the drug with the most potential to be successful should receive priority. There are several methods that can be used as evaluation tools in pipeline assessment; the challenge is to choose the right number of approaches, since each one in its own ways assesses risk and returns relating to R&D portfolios to aid executive in strategic decision-making. The most standard approaches evaluate portfolios are mathematical frameworks with a value-driven approach, used to determine the optimum size to maximize the value of the portfolio under budgetary constraints: namely, optimizing objective functions given a set of constraints. Portfolio valuation in the pharma sector involves sizing R&D portfolio as a function of expected revenues and making inclusion-exclusion decisions on a compound-by-compound basis¹⁴⁷. “Computationally

¹⁴⁶ Kester et al. (2011) as cited by Jones (2016)

¹⁴⁷ Evans, R., Hinds, S., & Hammock, D. (2009). *Portfolio analysis and R&D decision making*. Nature Reviews Drug Discovery, Vol. 8(3), pp.189-190.

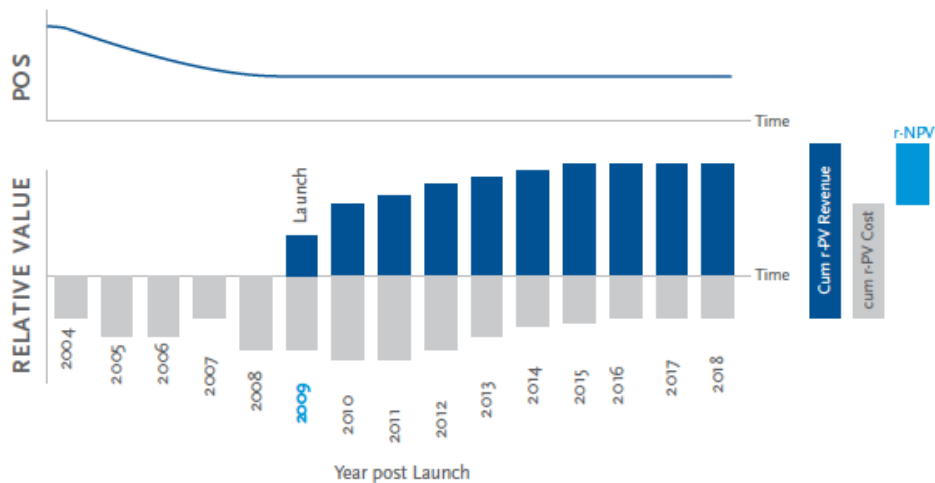
intensive approaches” are usually the best suited to manage the complexity “brought by the projects’ dependencies, pipeline resources, and economic and technical uncertainties; each of (the projects) must be managed before a sequence of new product development projects maximizing the expected economic returns at an acceptable level of risk for a given level of resources”

The most common methods include:

- *Discounted cash flow (DCF)* – the present value of a company’s future cash flow calculated as the forecasted annual earnings over the discount rate, weighted average of the cost of raising capital by issuing debt or equity is a useful capital budgeting tool.
- *Net present value (NPV)* – defined as the present value of future cash flow minus the initial investment. Projects are therefore ranked according to the financial value determined by this metric, from the highest positive down to the lowest. Evans et al. (2009) criticizes this method because it fails to distinguish between projects offering the same level of return but with different risk profile. Moreover another important drawback is that it fails to consider the risks associated during clinical development. To address these shortcomings, in light of the substantial uncertainty around safety, efficacy and quality inherent in biopharmaceutical R&D, the *r-NPV* (risk-adjusted net present value), has been introduced. This valuation method multiplies the cash flows by their respective likelihood of occurrence taking into account historical data on development success probabilities¹⁴⁸ (Figure 47,48). By doing so the valuation model incorporates the risks by creating different scenarios, from more optimistic to more pessimistic, to take into account the inherent risks of the business. The discounted cash flows obtained from each scenario is weighted by the likelihood of occurrence and then summed together.

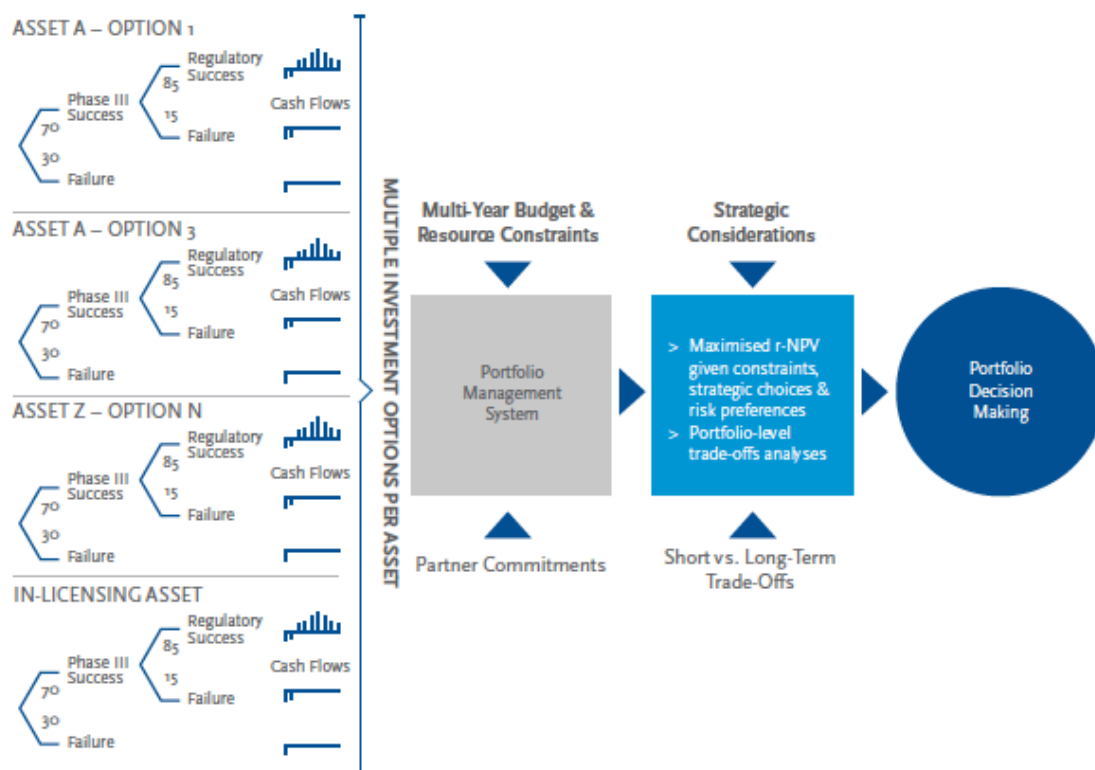
¹⁴⁸ Quintiles, *Strategic Portfolio Management & New Influencers in R&D Decision-Making*, White Paper, 2013.

Figure 47 Typical Project r-NPV



Source: Quintiles, 2013.

Figure 48 Traditional Portfolio Management Process



Source: Quintiles, 2013.

Nowadays development success probabilities alone are not sufficient, because firms are aware of the fact that demonstrating to regulatory agencies just a product's safety, efficacy, and quality is no longer

sufficient; to ensure success in the marketplace they must now demonstrate both clinical effectiveness – *Is the new product superior to the currently available alternatives, including no treatment (BSC)?* – As well as cost-effectiveness – *Is the product good value for money?*

“Portfolio methodologies have naturally evolved to also consider success probabilities of achieving the optimal differentiated value of a product, which will support reimbursement and an acceptable market share at a price commensurate with a minimum rate of return. [...] (Comparing) two products of similar r-NPV, developing a product for a disease with a high unmet need or lower precedents of value would carry less risk than developing a product with a low unmet need or higher precedent of value, should the likelihood of meeting the targeted product profile be identical.” (Quintiles, 2013, p.10)

- *Decision tree analysis* – useful as an illustrative tool for R&D decision points, the success probabilities and the potentially resulting decision options. Decision trees allow undertaking complex decisions with full consideration of success or failure probabilities.
- *Real options* – The options approach to project valuation seeks to correct the deficiencies of traditional methods of valuation – net present value (NPV) and DCF – by promoting the recognition that active management and managerial flexibility can bring significant value to a project¹⁴⁹. The results of a study by Hartmann and Hassan (2006) indicate real option pricing has not witnessed a high rate of adoption within the pharma industry. However, it has been mainly criticized for being effectively only for single projects, while in pharma a portfolio is formed by picking up multiple projects across different therapeutic areas. Real options may belong to one of several categories: growth, expansion scale, timing, switch processes, contract scale, and abandonment.

“Allocation of R&D resources is a critical component in a company’s overall strategy, (...) poor management of the innovation process can have huge long-term economic and strategic implications” (Duelli et al., 1998, p.11). However, the prevailing focus of portfolio management must expand to encompass more than just resource allocation. Today’s economic environment is tough and increasingly focused on customer value, whilst innovative products are complex, and competition is tough and multifaceted. The challenge is therefore maximize return on investment (ROI) by choosing products that contribute to sustainable profitability changing the business focus of portfolio management from mere financial metrics to a business model that maximizes customer value¹⁵⁰. The real value of an organization’s portfolio requires a holistic view beyond financial metrics that considers both the business strategy and fit within the organization’s business model, as well as it takes in to

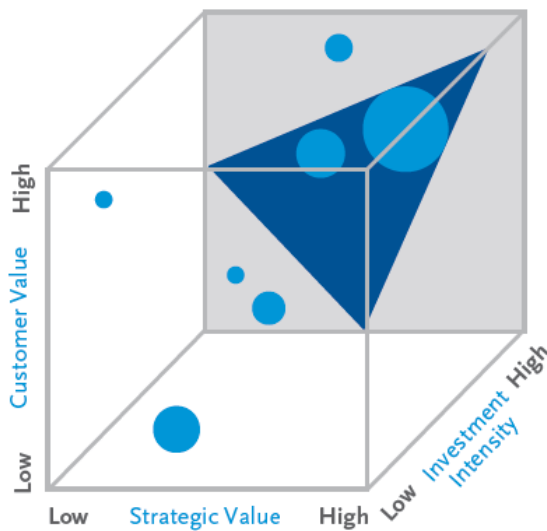
¹⁴⁹ Jekunen, A. (2014). *Decision-making in product portfolios of pharmaceutical research and development – managing streams of innovation in highly regulated markets*. Drug Design, Development and Therapy, 8, 2009–2016.

¹⁵⁰ Quintiles, “Strategic Portfolio Management & New Influencers in R&D Decision-Making”, 2013.

consideration the views of all stakeholders¹⁵¹. To obtain the optimum selection and balance in a portfolio, firms must first understand where and how markets will develop over the medium and long term as well as recognize the different stakeholders' requirements, their influence and the weight of their needs such that they can become an integral part of the organization's strategy, which is followed also through to R&D planning¹⁵².

In this context Mello et al. (2006) proposed a useful tool to determine what products to pursue by looking at the intersection of three axis: customer value¹⁵³, strategic value in terms of alignment with the overall business strategy and investment intensity which depend according to the specific assets and market in which the company operates (Figure 49). The optimal investment area is the sweet spot at the intersection when the three indicators are at their maximum value.

Figure 49 Tool to Identify the Sweet Spot for New Portfolio Projects



Source: Quintiles, 2013.

The combination of portfolio decision-making metrics of strategic fit, investment intensity and customer value is likely to lead management to make better-informed decisions, enhance the efficiency of R&D resources and provide a solid foundation for communicating product value to external decision makers. “Organization looking

¹⁵¹ It includes the payer, healthcare providers, patients, and patient associations.

¹⁵² For example, if the firm business model is focused on meeting unmet medical needs, the organization requires a portfolio that ensures a leadership position versus the competition with value demonstrated through improved patient outcomes. If the business is, however, focused in the generic market, a business model based on demonstrating quality and value without compromising patient outcomes must be required.

¹⁵³ In the biopharmaceutical industry the customer is not merely the patient but it encompasses a spectrum of different stakeholders. In an environment increasingly more focused on cost containment measures, in which payers have become central actors the value of a new medicine must be addressed not only in terms of clinical benefits of the treatment, but also in terms of QoL and socio-economic benefits. Furthermore value is perceived relative to current standard of care present in the market; indeed $V = R \pm D$. With $V = \text{Value (Price)}$, $R = \text{Price of reference product (Gold standard therapy)}$ and $D = \text{Net value of the perceived differentiation}$.

to evolve their portfolio management approach therefore need to translate payer-related strategic considerations into measures of value and overlay these with the traditional portfolio decision-making metrics. [...] With the growing concern regarding budget impacts and the pricing of products by healthcare systems, such a transition is, however, imperative. A process of reassessing the pharma-economic case for a drug underpinning each stage of drug development is required to contribute to the decision whether or not to proceed to the next clinical stage and, ultimately, to reimbursement and market entry.” (Quintiles, 2013, p.12)

2.4.3 Portfolio Management Process

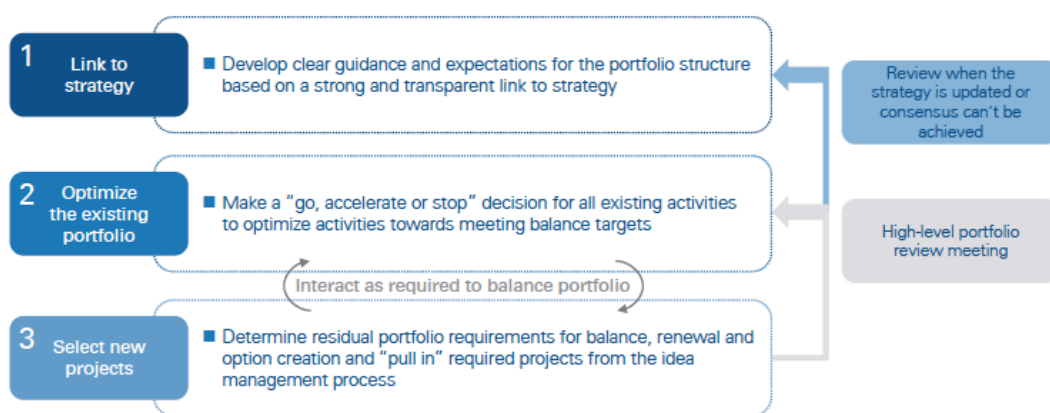
Innovative industries, such as the biopharmaceutical sector, are aware of the importance of portfolio management and that an effective strategic management of both their R&D pipeline as well as business portfolio is necessary for the long-term renewal and competitiveness. “In an industry where innovation and time to market are the key determinants of success, the companies who best manage their innovation efforts stand to gain at the expense of their competitors” (Duelli et al., 1998, p.11). When managing a portfolio, indeed, funding decisions are extremely important for establishing long-term growth and making the wrong ones can be devastating for a firm’s budget¹⁵⁴: “deciding on the right portfolio can mean the difference between remaining competitive and falling behind” (Jones, 2016, p.4). For this reason organizations have started to recognize the importance and establish a credible tailored dialogue decision process across their global organization for portfolio management, which should provide “a systematic method for evaluating, prioritizing, and investing in the best research projects, and then driving these projects through the development stage to generate profitable products” (Duelli et al., 1998, p.2). Jones (2016) reports that organizations with an effective portfolio management process in place have 62% of products that meet or exceed return on investment (ROI).

Unfortunately companies do not own unlimited resources and they must ensure that all projects obtained the necessary resources to be successful; if these are not available at that moment they are either postponed or discarded. Portfolio strategy decisions are therefore made throughout a custom-tailored decision process that varies in terms of requirements from company to company but it is structured in a common way – through individual projects reviews at predetermined stage gates combined with an entire portfolio review – to answer to similar needs in terms of resource allocation and product prioritization. Bode-Greuel and Nickisch (2008) specify that in the pharma industry the portfolio management process entail stage-gate decision checkpoint, related to the major preclinical and clinical development milestones, when progress is measured and it is decided whether the achieved results support the continuation of development or the project should be reprioritized.

¹⁵⁴ Kester et al. (2011)

Decision-making is one of the core functions of any drug development company, essential for determining the firm’s long-term success. In fact, a company’s portfolio can only become successful when supported by the right decisions. Therefore it is imperative that an efficient portfolio management demands effective decision-making. Decisions must be coordinated following a process plan fully integrated with the company strategy, through preplanned decision points and that needs to be constantly updated. Bearing this in mind, Arthur D. Little in an R&D management best-practices case study of 2015, highlights the three sequential steps of to follow for a successful portfolio management process (Figure 50):

Figure 50 Arthur D. Little Portfolio Management Process

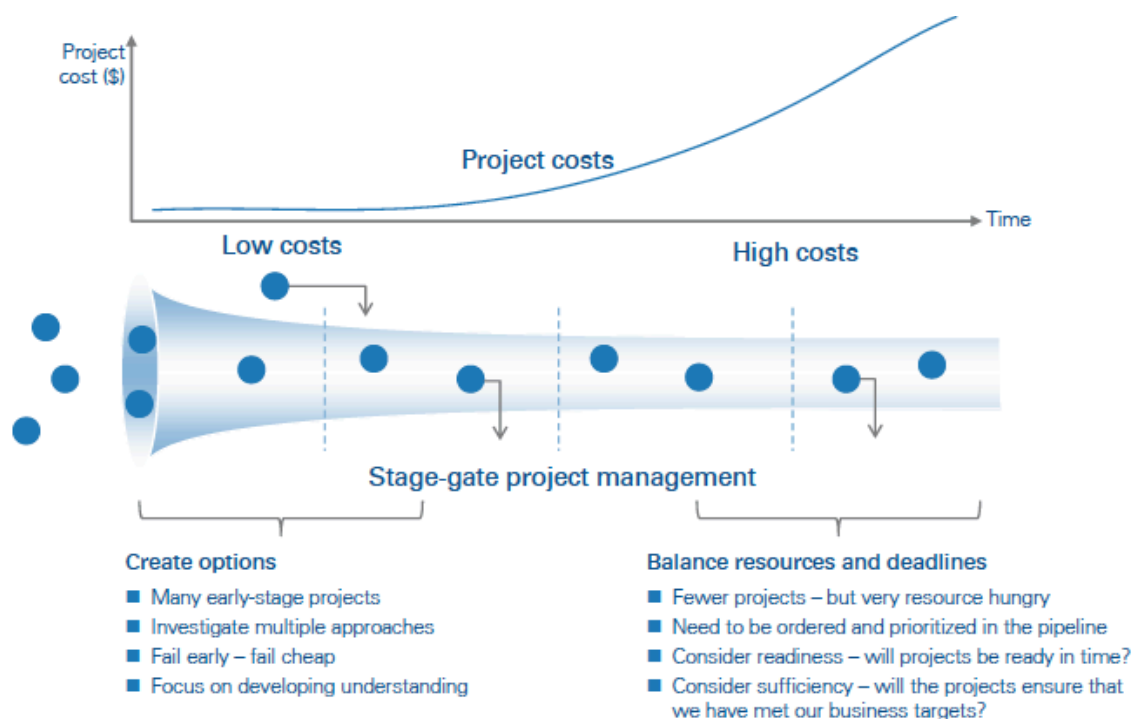


Source: Arthur D. Little, 2015.

- 1. Link to strategy.** “Critical to the success of the portfolio management process is the direct link to the corporate and/or business unit strategy of the company” (Duelli et al., 1998,p.2). Indeed, companies should structure their portfolio in a way that it is clearly aligned with the corporate and product strategy. R&D portfolio should in fact not only be balanced but also focused on strategic goals otherwise the risk is to crawl towards the safe zone of incremental innovation, with the risk that the market will shift in a few years and you won’t be able to respond. Portfolio management is central to ensuring that strategy is reflected in the mix of projects arriving at stage-gates.
- 2. Optimize the existing portfolio.** Stage-gate review steps should be clearly defined as projects go from early research to late stage development in order to lead to portfolio-review decisions, in which projects no longer in line with the strategy or that do not contribute to the portfolio-balance, should be eliminated. Portfolio-review can occur at two separate levels: a high-level strategy review, in which a common perspective on the portfolio strategy is discussed, and a deeper review that identifies whether the single activities are in line with the strategy. During this process resource allocation is crucial (Figure 51); in a stage-gate portfolio management in the early stage development priority allocation is not the primary focus as costs are low while risks and uncertainties are reasonably high. The aim of this

first part of the process is to quickly identify projects not suitable to proceed through late stage development and later commercialization in order to ensure that failures are as early and cheap as possible. In a late stage development, instead, projects have been accurately financially valued¹⁵⁵ and they are very resource-hungry, this explains why they must be ordered and prioritized. Prioritization, both in terms of readiness and sufficiency, becomes appropriate because selection is limited by resources availability and budget constraints to sustain multiple projects simultaneously.

Figure 51 Project Management Stage-gate Process



Source: Arthur D. Little, 2015.

“A portfolio must be dynamic – changing and evolving with time, tracking the progress of R&D projects while following changes in a company’s strategy. Avoiding or postponing decisions can be as dangerous as making poor ones. (...) It is the portfolio management process, guided by the strategy that provides the discipline to overcome this and have an element of appropriate competition between projects. Frequently the greatest challenge around the management of portfolios is not defining what must be done in the future, but dealing with what has gone before. Cleaning the portfolio, removing legacy or failing projects, requires regular action – too often the failing figurehead projects of yesterday are left redundant, blighting the current portfolio by sapping limited resources. Removing these (...) ensures application of adequate resources to each project, which provides greater momentum, improved efficiency and much reduced time to market.” (Arthur D.Little, 2015, p.12).

¹⁵⁵ Focus on financial valuation is reasonable in late stage development but it is worth noting that firms rely on different methods, most of which non-financial, e.g. link to strategy and market entry timing.

3. **Select new projects.** Considering the portfolio balance and requirements a steady stream of ideas, well aligned with corporate goals and a strong link to strategy should result long the process. Ideas should be pulled forward into the stage-gate process based on portfolio needs, rather than pushing them based only on the assessment during the idea-management process.

This highlights how the general portfolio management process should be designed within each corporation. It is key also to stress the importance of appointing an independent committee of senior executives in charge of the different stage-gate review moments set up along the process in order to decide which projects are worth progressing and which, instead pull the plug. The independent committee is supposed therefore to maintain an objective point of view during the evaluation process. Furthermore the exercises of portfolio valuation, highlighted before during the chapter, are not supposed to be performed only once or twice a year, but instead portfolios should be reviewed constantly in order to maintain balance between the overall risk and its potential value: “drug candidates aren’t as volatile as share. Nevertheless, a clinical pathway can be completely redesigned in six months (...) so it’s crucial to monitor the drug portfolio continuously and dynamically – and to be decisive” (Pwc, 2012, p.35).

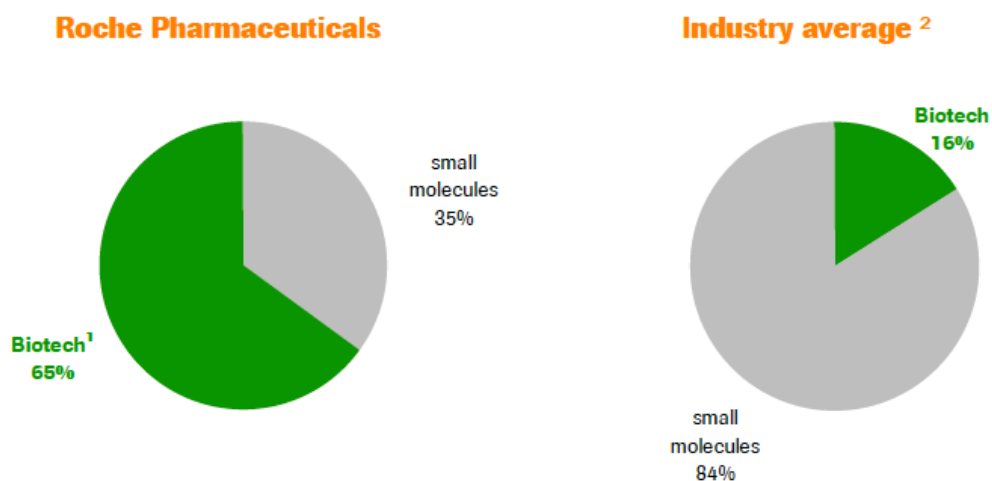
So far it has been stressed the importance of putting in place a sound portfolio management process, able to lead to effective strategic decision-making in order to carefully maintain a balanced heterogeneous product R&D pipeline and product portfolio. The discussion has outlined the most common standardized approaches, both qualitative and quantitative, employed in portfolio analysis and how a bulletproof portfolio management process should be structured. Whenever the firm’s portfolio is analyzed and judged unbalanced the firm has different strategic options to pursue: either it may grow capabilities in-house leveraging on its internal R&D to generate the next blockbusters or more frequently rely on external growth strategies to shorten the time-to-market.

3 A Closer Look at Hoffman- la-Roche

3.1 Company Overview

F. Hoffmann-La Roche, or simply Roche, is one of the leading research-focused healthcare groups worldwide. Headquartered in Basel, it is engaged in the discovery, development and commercialization of innovative diagnostic and therapeutic products¹⁵⁶. Roche is one of the world’s largest biotech companies, with 17 biopharmaceuticals on the market and a large and diverse portfolio of biopharmaceuticals in pipeline, compared to the industry average (Figure 52).

Figure 52 Roche Pharmaceuticals classification



Source: Severin Schwan, 2010.

As a biotech company, Roche is the frontrunner in personalized healthcare, focused on combining target therapies with companion diagnostics. In fact, the group can leverage on two business divisions: pharmaceuticals and diagnostics. In the first half-year result in 2017, approximately the 80% of the group total sales are however generated by the pharmaceutical division, which only in the last year grew of 5% (Figure 53).

¹⁵⁶ MarketLine, *Company Profile F. Hoffman-La Roche Ltd*, June 2017.

Figure 53 Roche HY 2017 Results

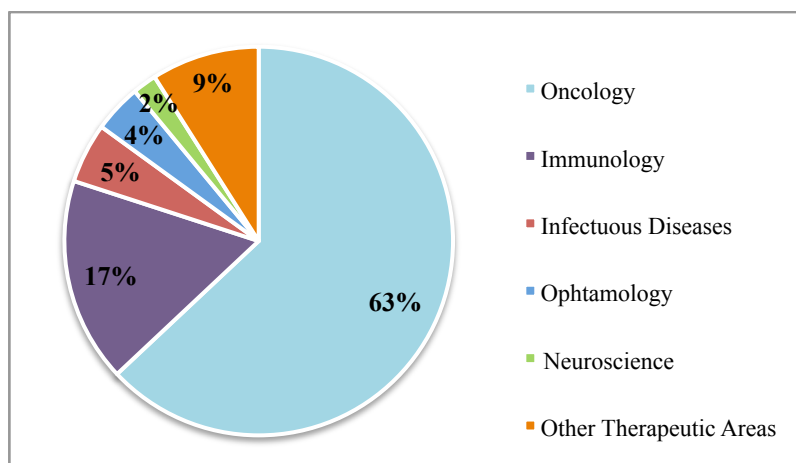
	HY 2017	HY 2016	Change in %	
	CHFbn	CHFbn	CHF	CER
Pharmaceuticals Division	20.5	19.5	5	5
Diagnostics Division	5.8	5.6	5	5
Roche Group	26.3	25.0	5	5

Source: Half-Year Results, July 2017.

Two main therapeutic areas drove the pharmaceutical division’s sales growth: oncology, with HER2 breast cancer medicines, and in immunology, through Actemra/RoActemra.

The group can count on several truly differentiated marketed products in five main therapeutic areas: oncology, immunology, ophthalmology, infectious diseases and neuroscience. Oncology is by far the largest therapeutic areas in which Roche operates, generating approximately 60% of its sales in 2014 (Figure 54). Roche is a worldwide leader in oncology thanks to its innovative target therapies, which are able to selectively tackle biomarkers and therefore increase both the quantity and quality of life of numerous patients affected by different cancer types: breast, colorectal, lung, non-Hodgkin lymphoma, chronic lymphocytic leukaemia.

Figure 54 Roche's Sales by Therapeutic Area, 2016



Source: Elaborated from Roche Website Data.

Over the years Roche has developed and commercialized numerous molecules that have contributed to improve patients' overall survival as well as their quality of life. Still today, six out of the ten top-selling Roche's pharma medicines, in terms of global sales generated in 2016, belonged indeed to the oncology business (Figure 55).

Figure 55 Top-selling pharma products in 2016 (CHF billion)

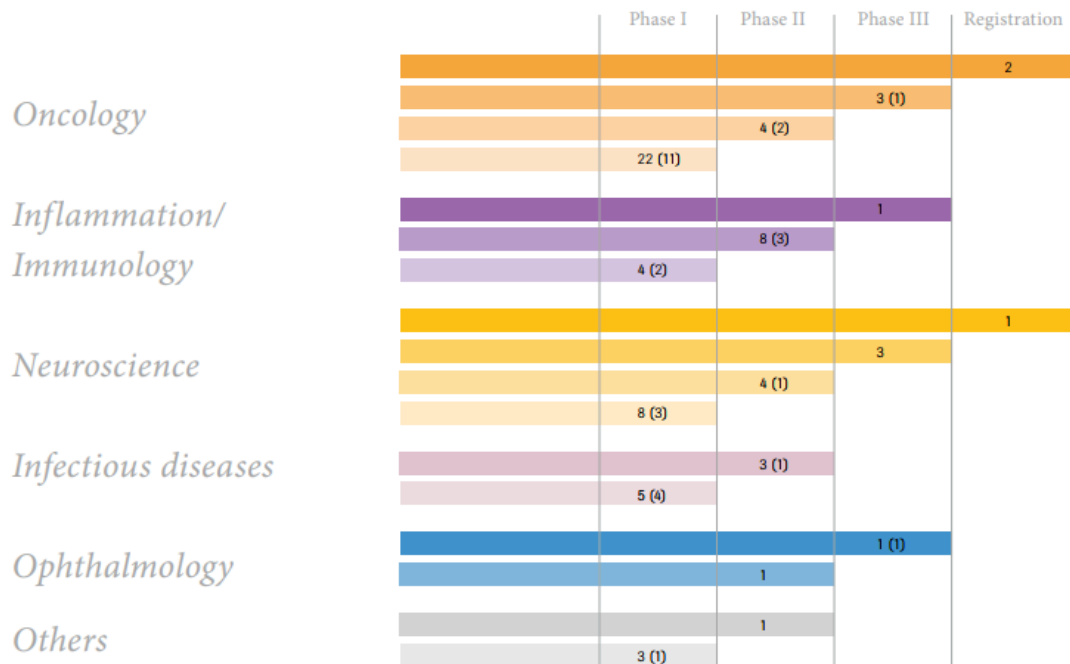
Global Sales of top 10 Medicines in 2016	CHF billion
MabThera/Rituxan 1,2	7.3
Avastin 1	6.8
Herceptin 1	6.8
Perjeta 1	1.8
Actmra/RoActemra 2	1.7
Xolair 2	1.5
Lucentis 3	1.4
Activase/TNKase	1.1
Tarceva 1	1.0
Kadcyla 1	0.8

1. Oncology, 2. Immunology, 3. Ophtamology

Source: Elaborated from Roche Investor Update, 2017.

Roche's personalized healthcare strategy aims at providing medicines and diagnostics that enable tangible improvements in patients' health, quality of life and overall survival. For this reason, in addition to its marketed products, Roche has invested in its pipeline, which today is one of the strongest drug development pipelines in the industry, comprised overall of 74 NMEs covering a broad range of diseases (Figure 56).

Figure 56 Pharmaceutical Clinical Pipeline



Source: Roche Annual Report, 2016.

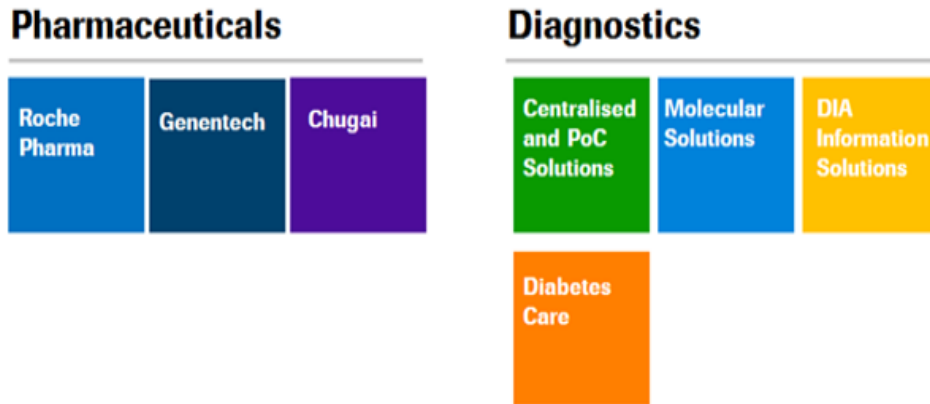
As previously mentioned, Roche keeps its Pharmaceuticals and Diagnostics divisions¹⁵⁷ under the same roof, which both operates on the most cutting-edge frontiers in order to continuously contribute to healthcare improvements, making Roche ideally positioned to drive personalized healthcare forward.

In the pharmaceutical division Roche pursues a decentralized research strategy, operating three large and independent research facilities (Figure 57): Roche Pharma (pRED) in Basel, Genentech (gRED) in USA and Chugai in Japan. Roche believes that “this diversity increases (its) chances of discovering new active substances. Upon achieving proof of concept in the clinic, all three research units pass molecules to the Pharma division, which (selects) and develops them into medicines” (John Reed Interview, 2017, pp. 6-7) Roche's innovation network in the pharmaceuticals division thus comprises the complete ownership of Genentech since 2009, leader in biotechnologies, and majority stake in Chugai. The relationship with Chugai started out as a strategic alliance in 2002 and it is the outcome of a merge between Roche Japan and Chugai with the objective to create a leader Japanese pharmaceutical company in prescription drugs. Furthermore, the company’s research capabilities are augmented by collaboration and worldwide alliances with universities, research institutes and biotech companies, that help Roche developing individual products and expand its product portfolio (Figure 58). This

¹⁵⁷ For the purpose of this thesis, I will focus only on the Pharmaceutical division.

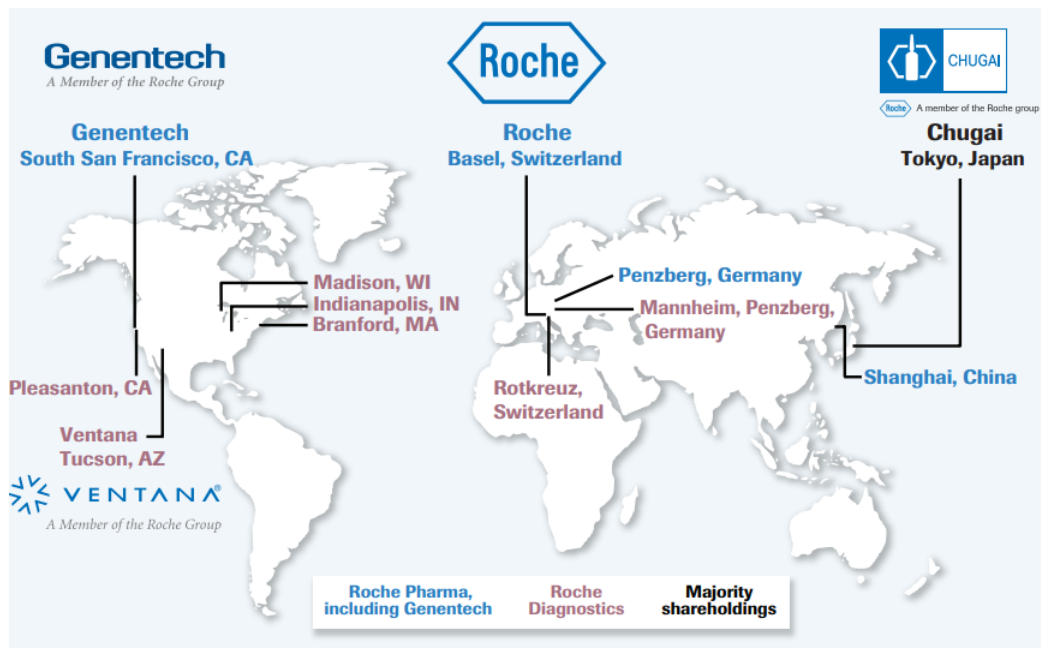
network thus promotes diversity in research approach, allowing access to new technologies and promising drug candidates.

Figure 57 Roche Business Structure



Source: Roche Italy Website

Figure 58 Roche Innovation Network



Source: Roche Investor Relations, 2015.

“At Roche, we have long valued external innovation as a critical component of our R&D strategy. A significant proportion of our sales is driven by products born of research partnerships, and 45% of our current pipeline comprises partnered products. Now, more than ever, collaborations are critical to realize the potential of personalized healthcare as well as enhance our pipeline in key disease areas. We have exceptional alliances across our therapeutic, diagnostic and

technological areas, helping us better understand and leverage complex biology, find new drug candidates, and make best use of a growing volume of genomic and real-world data.”

Annual Report, 2016, p.54

3.1.1 SWOT Analysis

Thus one of Roche’s main strength is the ownership of a solid product portfolio, which provides a high degree of diversity in terms of business opportunities and shields the company from market risks associated to singular product downturns. Moreover its marketed product portfolio is continuously fuelled by a strong investment on R&D that leads to an innovative and cutting-edge pipeline.

Table 2 Roche SWOT Analysis

Strengths	Weaknesses
Strong R&D capabilities help Roche in keeping its product pipeline robust	Dependence on mature markets
Wide product portfolio	
Opportunities	Threats
Developments made by the group in its key pharmaceutical products	Biosimilars could be a long-term threat to Roche's mAb therapies
Launch and approvals for new diagnostic tests and molecular testing systems	Cost containment pressure in healthcare spending
Strategic acquisitions would help the group in its business growth.	Regulatory compliance problems could affect the group's operating costs.

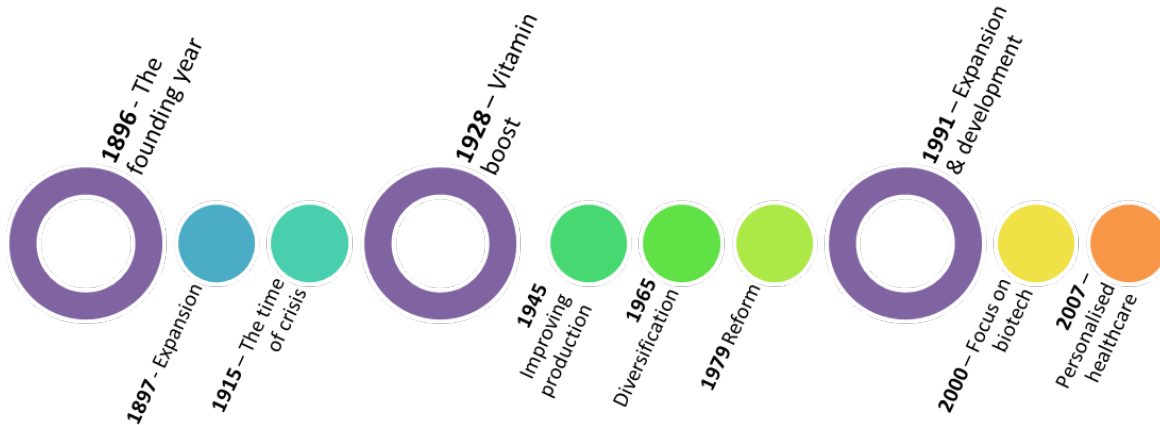
Source: Elaborated from MarketLine, 2016

Table 1 hints what are Roche’s weaknesses as well as its opportunities and threats. The overdependence on established markets has force Roche as well as many other pharmaceutical companies to expand into emerging markets, which can still sustain growth. In this context Roche is diversifying internationally by providing access to medicines through new reimbursement mechanisms and pricing strategies. Nowadays the oncology market is getting more and more crowded and radical innovations are getting harder to come by. Therefore Roche is expanding its existing product portfolio to new therapeutic areas such as the neuroscience, in which there is still room for scientific improvement as well as financial return for pharmaceutical companies. At the same time, Roche has the incredible opportunity to launch new innovative drugs together with a diagnostic companion, which can increase the probability of regulatory approval as well as access to patients.

As far as coming threats are concerned, the environment in which Big Pharma have to operate is becoming more challenging due to the cost containment pressure from the healthcare systems, blockbuster patents' expiration is putting at risk pharma current business model and overall competition is getting fiercer. Roche major threat is surely represented by the potential competition from biosimilars that will (or already have) jeopardize its blockbusters biotech products at patent expiry, putting at risk Roche's sales and profits in the long term.

3.1.2 Roche Milestones and Portfolio Evolution

Figure 59 Roche Milestones through History



Source: Elaborated from Roche Website

F. Hoffmann-La Roche & Co. was founded at a time when industrial revolution was changing the face of Europe. On October 1, 1896, at the age of 28, Fritz Hoffmann-La Roche, a pioneering entrepreneur, launched his company as the successor company to Hoffmann, Traub & Co in Basel, Switzerland. He was among the first to recognize that the industrial manufacture of medicines would be a major advance in the fight against disease. Since then, Roche has grown into one of the world's leading healthcare companies.

Roche soon expands its business activities worldwide: from 1897 to 1914 it builds a network of European and overseas agents and subsidiaries. During this period it strives for strong cooperation between academic circles and commercial developers that to the expansion of its portfolio to include the analgesic and hypnotic *Pantopon* (1909) and *Sedobrol* (1912) a drug for epilepsy and nervous disorders among many.

The First World War has devastating repercussions for Roche. The German boycott of its products, Basel's isolation from its plant in Germany, the loss of the company's Russian market and assets in the revolution of 1917, and sizeable foreign exchange losses altogether combine to create a financial crisis. Additionally, Roche regrets the death of founding father Fritz Hoffmann in 1920. A glimmer of hope arises when Markus Guggenheim publishes a classic study of biogenic amines, which Roche begins marketing and call biochemicals. These biochemical, which include proteins, vitamins and hormones, enhance Roche's standing in the scientific community.

Roche managed to overcome the crisis and experiences an unexpected upsurge spurred by its vitamin production, which made the return to former prosperity possible. It becomes the leading suppliers of vitamins, having also mastered the industrial synthesis of vitamin A,B1, B2, C,E and K1. By 1938 vitamins are the company's mainstay, encompassing *Benevra*, *Redoxon*, *Nostravit*, *Beflavin* and *Epynal*.

Vitamin output increases and new production locations strengthen Roche's position as one of the main producers of vitamins. To avoid a strong dependency on vitamins, however Roche intensifies its pharmaceutical research. During this period, Roche's researchers discover a compound of the benzodiazepine class that sedates without causing drowsiness. Tranquillizers., therefore, soon become one of Roche's most important product segments; this segment together with a push to streamline vitamin production fuels a period of unprecedented growth.

Between the early 1950s and mid-1960s pharmaceutical research is extremely diverse, with a portfolio of pharmaceuticals ranging from tranquillizers and antimicrobials to agents for cancer chemotherapy. In 1962 Roche introduces its first anti-cancer drug, *Fluorouracil* that paves the way for Roche's activities in the field of cancer chemotherapy. *Valium*, a sedative and anxiolytic drug that will prove to be a therapeutic success, launches in 1963 enabling Roche to build a worldwide reputation in psychotropic medications. In the same year Roche acquires Givaudan SA, a leading manufacturer of fragrances and flavors and a longstanding customer for intermediaries from Roche's vitamin A production. It also acquires Roure Bertrand Dupont, a renowned French fragrance company, in 1964.

Propelled by the success of the benzodiazepines, Roche diversifies across the entire spectrum of healthcare. In 1968 Roche enters the diagnostic market with the objective to develop new diagnostic tests and automatic

analyzers. For this reason, in Switzerland and in the United States, bioelectronics departments are set up to develop electronic medical instruments.

This period also marks the start of Roche's involvement in basic biomedical research. The company establishes the Roche Institute of Molecular Biology in Nutley, a year later the Basel Institute for Immunology and then the Nippon Research Center in Kamakura, Japan.

Roche begins to tighten its organizational structure and moves towards creating separate business units. Corporate activities are however consolidated through acquisitions and divestments. After the corporate realignment, Roche operates with four core business divisions: pharmaceuticals, vitamins and fine chemicals, diagnostics, and flavors and fragrances. The corporate changes involve the formation of a holding company (Roche Holding AG), parallel to an increase in nominal share capital and in the number of bearer shares. Moreover, the new structure gives Roche the possibility to access international markets.

As far as product development is concerned, in 1980 Roche and Genentech, a biotech company based in San Francisco, begin a joint project that will lead to a leap forward in cancer therapy also throughout the year to come. In 1982 *Rocephin*, an antibiotic of the cephalosporin class is launched and by 1987 it outsells all other Roche products.

Through its commitment to research and innovation, Roche continues to make steady advances in drug therapy that will replace more expansive treatments and shorten hospital stays. A series of innovative blockbusters for cancer treatment are developed starting from the mid-90s: *Herceptin*, a humanized antibody designed to target and block the function of the HER2 protein produced by a specific gene with cancer-causing potential; *MabThera*, which increases the progression free survival for patients with adult leukemia; *Tamiflu*, an oral antiviral treatment that can be used both for prevention and treatment of influenza.

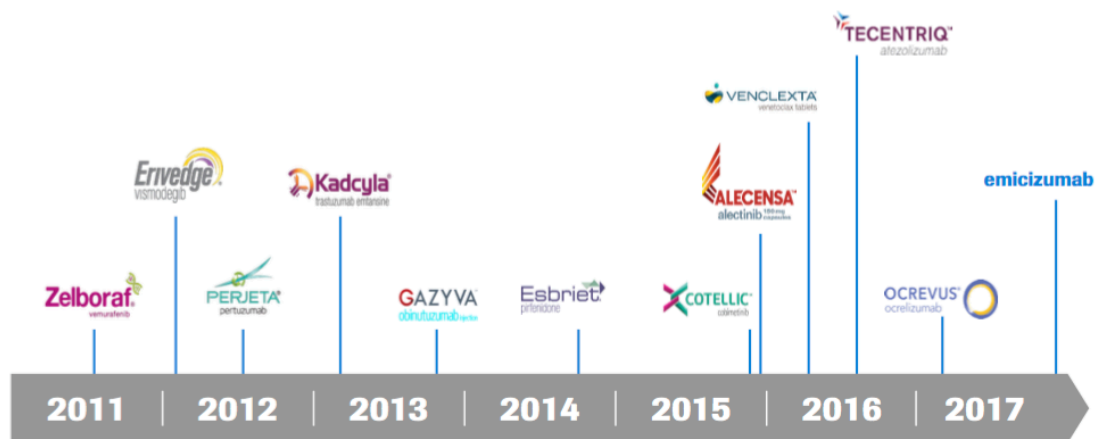
Roche strengthens its position in the US pharmaceutical markets by acquiring Syntex Corporation in 1994, which will later become Roche Bioscience, one of the group's major R&D site. The takeover continues Roche's strategy of concentrating on its core business. The purchase of Nicholas, a producer of non-prescription medicines, in 1991 strengthens Roche's portfolio of OTCs medicines, an increasingly important area because of the growing trend towards self-medication. Another important milestone for Roche in terms of M&A is the acquisition of Boehringer Mannheim in 1998. With this acquisition Roche becomes the world leader in diagnostic markets for its unique range of innovative products, depth and breadth of technologies and overall geographical presence.

To intensify its focus on healthcare, Roche divests two businesses: fragrances and flavors and vitamins and fine chemicals. The company therefore commits itself to innovation by concentrating only on its pharmaceuticals and diagnostic divisions, which supply products spanning the healthcare spectrum from early detection and prevention to diagnosis and treatment. Combining the strengths and expertise in both divisions, Roche plays thus an incredible role in shaping the future of medicine by contributing to the personalized healthcare approach.

In 2002 Roche Japan and Chugai enter into a strategic alliance to create a research-driven pharma company, the 5th largest pharma company operating in Japan that specializes in prescription pharmaceutical with strengths in biotechnology. As far as product development is concerned, two other blockbusters are launched: *Avastin* in 2004, an anti-angiogenic agent, and *Tarceva*, a TKI inhibitor.

As demand for innovative medicines steadily increases, Roche starts restructuring to focus more on biotech and decides to expand its manufacturing capacity. The increased focus on innovation and biotechnology leads to important advances in diagnostic techniques and medicines aimed at molecular targets. As a result, many diseases can be detected earlier and treated more specifically. The full integration with biotech pioneer Genentech within the Roche Group in 2009 makes Roche the world’s largest biotech company. Moreover, sharing intellectual property and technologies while maintaining a diversity and independence of research approaches enhances constant innovation. Other key players’ acquisitions in life science research, gene sequencing and tissue diagnostics also proved to be necessary to strengthen Roche’s access to innovation and new technologies and drive its commitment to more targeted treatments that, ultimately, make personalized healthcare a reality (Figure 60).

Figure 60 Past and Future Roche Launches



Source: Roche Analyst Event, 2017

Personalized healthcare (PHC) is indeed at the center of Roche business strategy and it is seen as a key enabler for delivering clinically differentiated medicines. A new unifying and inspiring Roche purpose statement is launched globally: *Doing now what patients need next.*

“Proud as we are of our past and present achievements, what really excites us, however, is the future.”

Severin Schwan, CEO

3.2 Roche Corporate Strategy

Pharmaceutical companies are facing an incredibly challenging environment: more stringent regulation, cost-pressures from payers and the concern of declining returns growth rate. Roche response to the challenges coming from the external environment is very clear: be focused on innovation, on true medical differentiation, on patients benefits, increasingly leveraging the synergies between its two core business (pharma and diagnostics) in order to thrive new tailored solutions in personalized healthcare while providing value for all its stakeholders. Roche’s key competitive advantage is, as a matter of fact, the leverage between Pharmaceutical and the Diagnostic businesses. Having the two business under one roof makes Roche uniquely positions in the industry; in particular allowing it to exchange know-hows and expertise at the very early stage of R&D, a situation in which any independent companies were to overcome many hurdles in order to enjoy the same advantage.

The key strategic drivers defined by Roche for its pharma division, through which it aims at succeeding in this challenging environment, are grounded in three main pillars that define Roche’s growth strategy¹⁵⁸:

- I. **Focus** on innovation, redefining the standard of care;
- II. **Expand** into emerging markets, improving patients’ access to medicines.
- III. **Protect** patients with high standards by ensuring governments set adequate guidelines for the development of biosimilars.

Pharma market growth rates have declined in the last decade; this has been triggered both by a bolus of patent expiration and by the fact that governments, on financial pressure, have set more severe pricing standards in terms of price reduction for in-marketed compounds and have become more demanding for new drug

¹⁵⁸ David Loew, Roche Investor Day (2012)

launches. Within this context Roche thanks to its innovative drugs and pricing approach, it has managed to significantly penetrate the emerging markets. Because of its focus on innovation, not only in developing new drugs but also in improving access through innovative pricing schemes, Roche has managed a strong performance in comparison to its peers mainly driven by organic growth. In fact, when compared to its peers, Roche has been recognized with 16 breakthrough therapies designations in cancer treatment since 2013 and this testifies its commitment to significantly advancing patients' care (Figure 61).

Therefore, despite the upcoming future patent expiration, which will negatively affect the net market growth, there is still growth potential, which Roche can definitely tap through its strong and highly differentiated pipeline.

Figure 61 Recognition for Innovation, 2013 - Present

16 Breakthrough Therapy Designations

Rank	Company	#
1	Roche	16
2	Novartis	12
3	BMS	10
4	Merck	9
5	AbbVie	7
5	Pfizer	7

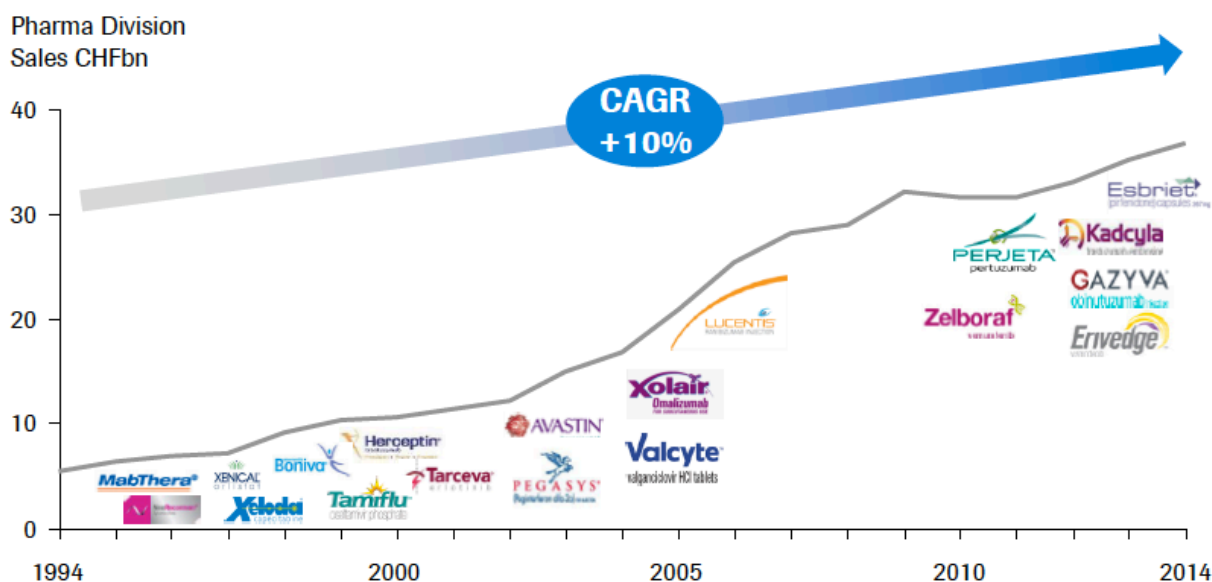
Year	Molecule
2017	Zelboraf (BRAF-mutated ECD)
	Rituxan (<i>Pemphigus vulgaris</i>)
	Actemra (<i>Giant cell arteritis</i>)
2016	Alecensa (1L ALK+ NSCLC)
	Ocrevus (PPMS)
	Venclexta (AML)
	Venclexta + Rituxan (R/R CLL)
2015	Actemra (<i>Systemic sclerosis</i>)
	Tecentriq (NSCLC)
	Venclexta (R/R CLL 17p del)
	Emicizumab/ACE 910 (<i>Hemophilia A</i>)
2014	Esbriet (IPF)
	Lucentis (<i>Diabetic retinopathy</i>)
	Tecentriq (Bladder)
2013	Alecensa (2L ALK+ NSCLC)
	Gazyva (1L CLL)

Source: Half-Year Results, July 2017.

3.2.1 Innovation and R&D in Roche

As outlined above, Roche has a strong track record of innovation; since the ‘90s through the past two decades, it has focused on large clinical unmet needs and on transforming the field of medicine. The fact that it will launch six new medicines in a two years’ time period demonstrates its commitment to innovation, in a moment when the company is facing competition to its core business. Despite recent competition, on the innovation side, Roche has always shown above-average R&D success rate (Figure 62).

Figure 62 R&D Productivity measured by Company Launches



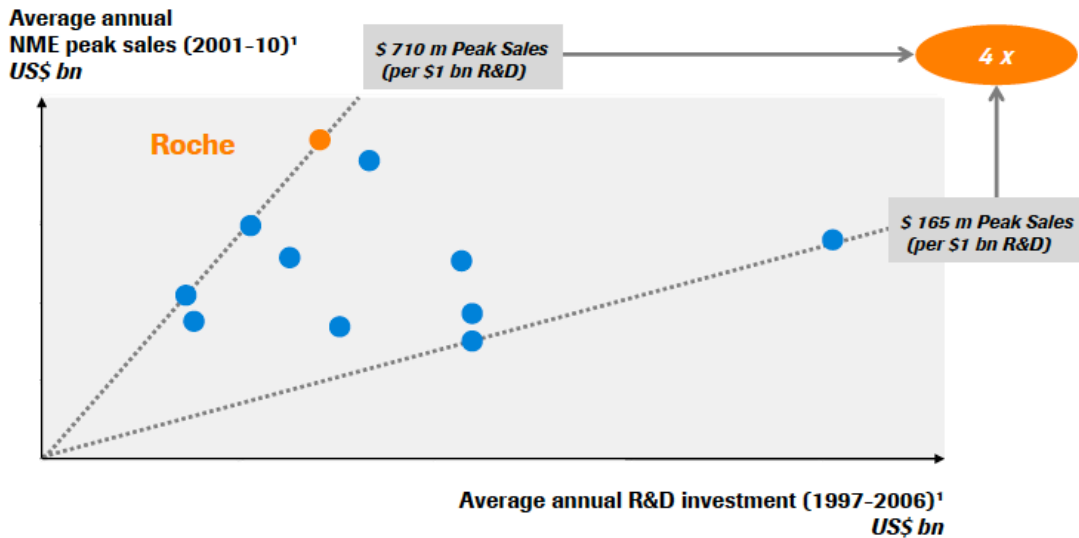
Source: Daniel O’Day, Roche Pharma Day, 2015.

A fundamental topic for the long-term success of the industry is definitely R&D productivity and this is also at the heart of Roche since its strategy is entirely founded on innovation. In the last decade R&D returns in the pharma industry, as previously highlighted, have been declining and studies would suggest that the industry overall is going through a critical zone earning approximately on average 8-10% return, which makes it hard for companies to even earn back their cost of capital¹⁵⁹. Nevertheless, what is really important for an investor is not the industry average, but the R&D productivity across the different players (Figure 63). In particular, when analysing the position of Roche over ten years period on the basis of its average annual R&D spending and the outcome of its investments in the form of NMEs, a 4x difference in productivity can be observed between Roche

¹⁵⁹ Daniel O’Day, Roche Pharma Day, 2015.

and its peers. In other words, the best performing companies get out four times for each single US\$ that is invested in R&D compared to the least performing companies.

Figure 63 Roche R&D productivity compared to peers

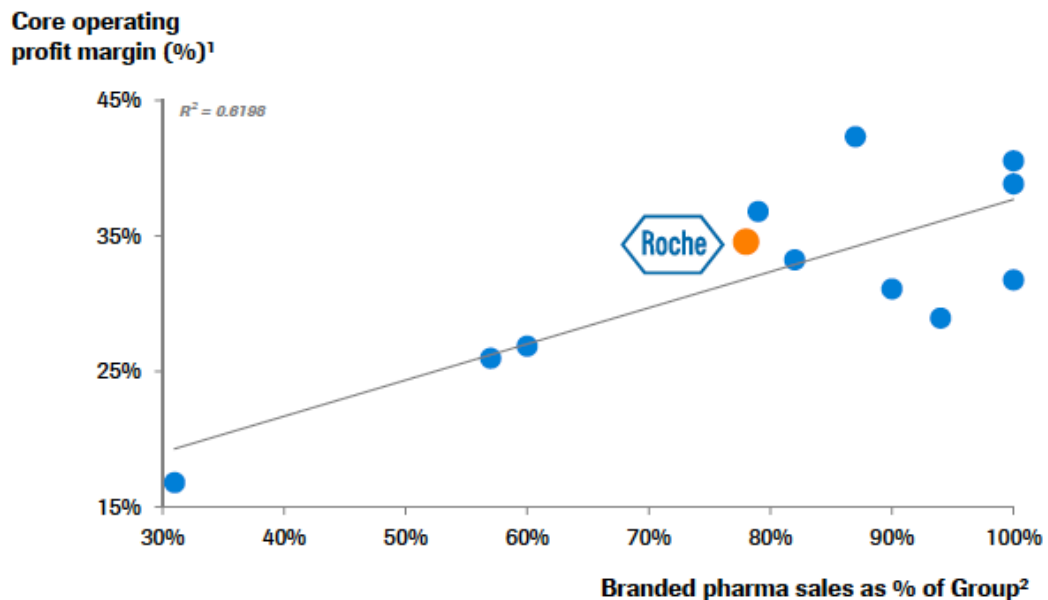


Source: Severin Schwan, Roche Investor Day, 2012

This R&D productivity challenge implicates an important fact: segregation will continue as only true innovation will be rewarded. Companies with marginally differentiated products that don't deliver their cost of capital won't be reimbursed from payers and will eventually disappear, causing a disruption in the market with generics companies on the one hand and companies that go for true medical innovation on the other hand.

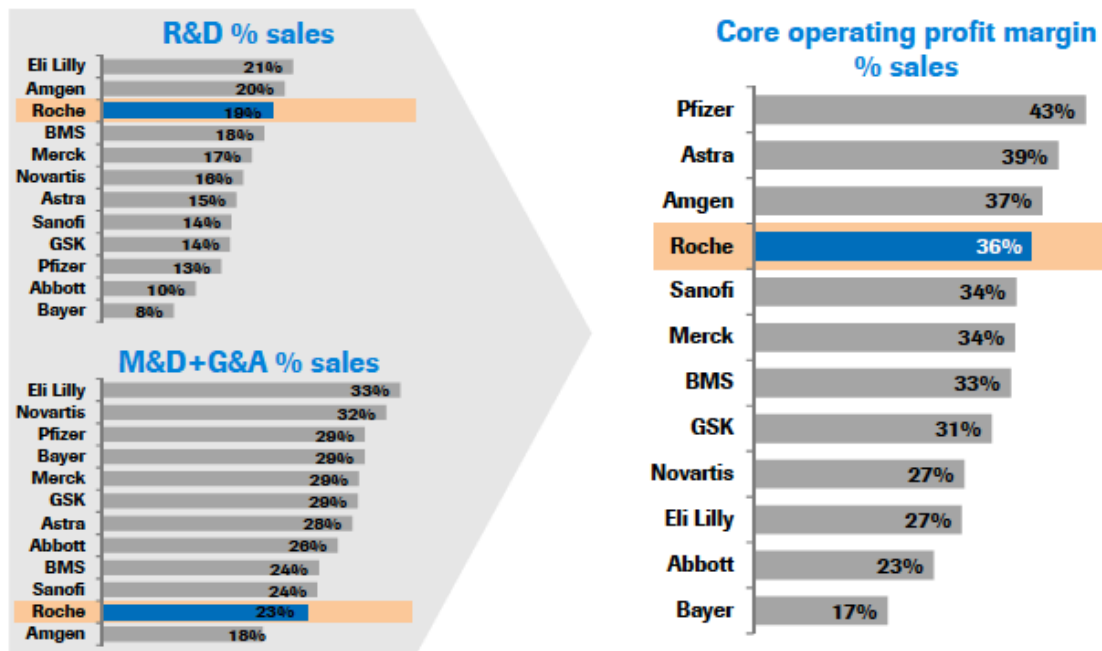
When looking at the profit margins and also the degree of diversification, it is very clear that the more focused a firm is, the higher margin it can earn in the pharmaceutical industry (Figure 64). What comes across from this insight is therefore the acknowledgment of how Roche, thanks to its strategy, appears to be well positioned among its peers, earning a good return as percentage of its sales also thanks to its low level of marketing, general and administrative expenses (Figure 65).

Figure 64 Differentiation Strategy vs Profit Margin



Source: Alan Hippe, Roche Investor Day, 2012

Figure 65 P&L reflects Roche's innovation-based strategy



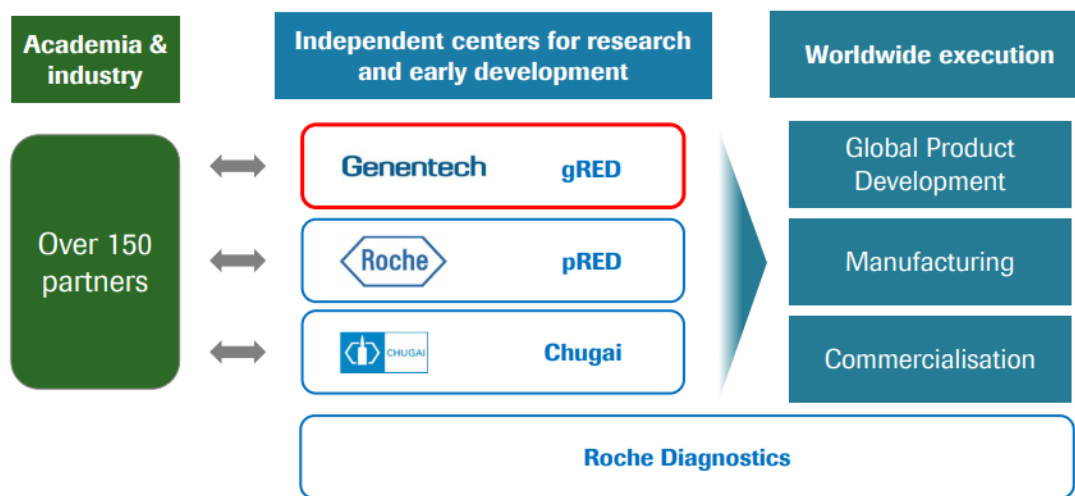
Source: Alan Hippe, Roche Investor Day, 2012

How does Roche manage its R&D? It possible to highlight three basic success factors¹⁶⁰:

- I. In-house cutting edge science:** this implies understanding the disease in order to increase the likelihood of selecting the right target and move the right opportunities through the pipeline. One possible indicator is patent application and it is clear that among its peers, Roche has a leading position. Its focus is on translating science into patient benefit and to do so Roche tries to provide a culture of empowerment and a decentralized management approach in decision-making. This is why Roche organized itself in decentralized units and kept its centres independent within the Roche Group.

The independent centres doing research and early development (RED) within the Roche Group are: Genentech RED (gRED), Pharma RED (pRED) and Chugai and a number of other small collaborations at arm-length (Figure 66).

Figure 66 Diversity of Approaches within RED in Roche



Source: Richard H. Scheller, Investor Day, 2012

The pRED and gRED organization represent the heart Roche's research and development that were established at the time of the Genentech integration in 2009 and have been kept separated since then in order to keep the vibrant culture alive and avoid the increase in complexity. They provide pivotal trial-ready molecules for worldwide execution to the global product development in the different disease areas, managing balanced portfolios, in which the majority of molecules are developed with a companion diagnostic in a personalized care approach. Despite the Genentech research and early development has been integrated within Roche in 2009, it still remains an independent environment in

¹⁶⁰ Severin Schwan, Roche Investor Day (2012).

which they receive their budget but run and manage their portfolio-decisions freely in order to maintain high Genentech's spirit of bringing innovation to patients.

- II. R&D resource allocation:** there are always more projects and opportunities than funds. This means that there must be constant trade-offs decisions; it must be decided early enough to invest enough resources in the most promising projects and likewise kill the less promising ones. The decision-making, the governance of how to allocate resources across the different opportunities is crucial.

“There is a huge difference in terms of decision criteria whether we speak about research and early discovery and late stage development. Of course it all starts with a medical need, but then in research it's very much about the plausibility of the scientific hypothesis, the expertise on the field you have in-house and it needs a lot scientific judgement whether you are on the right target. In contrast, if you are on late stage development process you have pre-clinical data – an analytical element. You have a better perspective on the market potential, the competitive landscape and on the feasibility of the manufacturing process.”

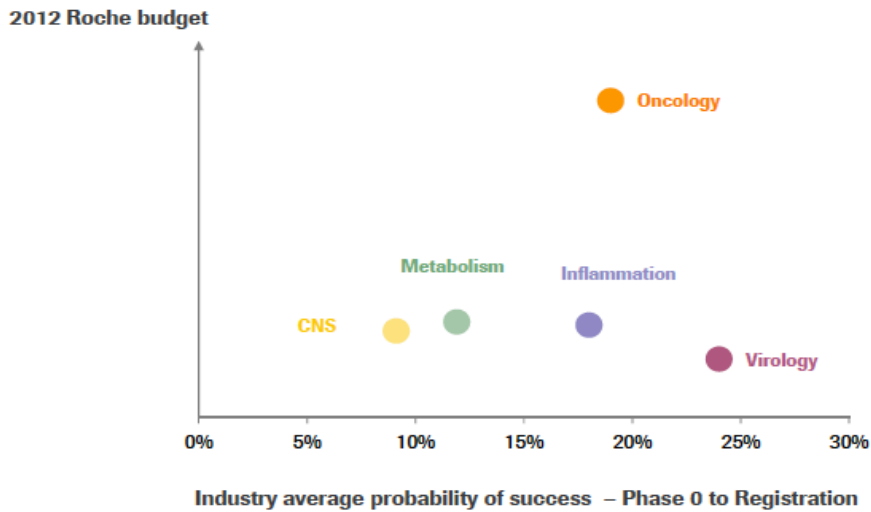
Severin Schwan, CEO, 2012

This distinction is important because it influences how, from the management point of view, the framework is set: at the early stage you rather leave freedom to the scientists to make the trade-offs within a given budget, whereas at a later stage you look at the specific opportunities in more analytical way.

Roche invests significantly in Research and Early Development, spending a considerable amount of its P&L on R&D, more than the industry average and any other company. Precisely it allocates approximately 60% of its budget on R&D, which it is spread across its decentralized hubs of innovation, relying on different research engines: Roche (pRED), Genentech (gRED), Chugai R&D, other pharma partners.

Furthermore, within R&D the vast majority Roche's R&D funds are distributed in oncology (Figure 67), around 50% with a relative high probability of success, that represent its bread-and-butter business with success rate above industry average. At the same time Roche is investing in other disease areas, such as CNS, that even though are characterized by very low probability of success will be the future clinical development frontier.

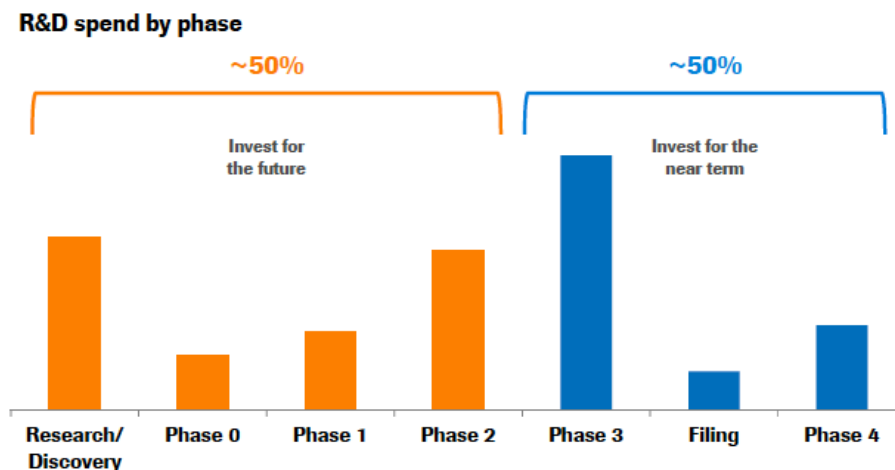
Figure 67 Roche's Portfolio from a Risk and Disease Point of View



Source: Alan Hippe, Roche Investor Day, 2012

Looking also at Roche's investments through the different stages of the value chain (Figure 68) the ratio is roughly 50-50 between the near term and the future. Furthermore, the vast majority of investments are done in phase II and Phase III when de-risking has happened already and success rates start to increase. Thus, from a portfolio point of view, Roche's R&D resource allocation can be considered well balanced and risk-adjusted between short and long term as well as within different disease areas; this intuitively shows how Roche is able to make the right portfolio decisions at the right time, which is to be attributed mainly to a clear, well-defined structure and governance in place for portfolio management.

Figure 68 R&D Spending in the Value Chain



Source: Alan Hippe, Roche Investor Day, 2012

“We are a innovation science-based company, but (...) we cannot win the game just on the base of efficiency, but we can free our funds and bring cash to areas where we have better returns. (...) Innovation drives sales growth; efficiency drives profitability and leads to cash generation and hopefully to a better value for this company because this gives us the opportunity to invest for the future and for the patients”

Alan Hippe, CFO, 2012

III. Continued focus on innovation: the right balance between internal and external innovation. Currently Roche has 150 on-going active partnerships and this is important for Roche since about a third of its total R&D pipeline compounds (phase I to III) as well as pharma sales stem from third parties relations.

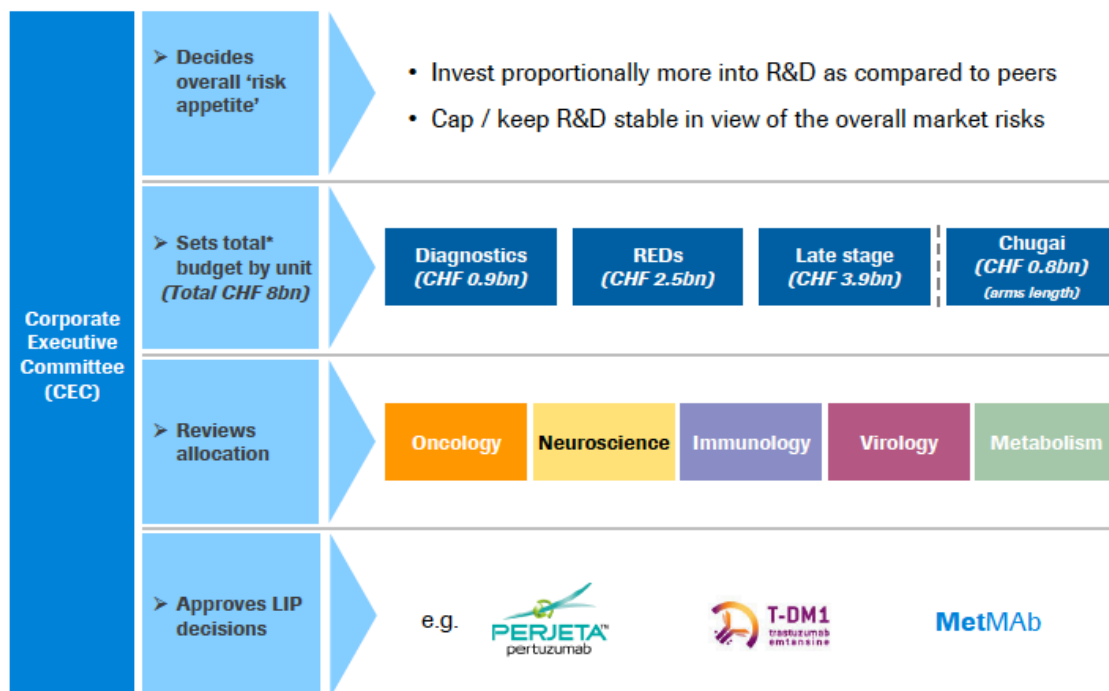
3.3 Portfolio Management at Roche

As we have already outlined before there are basically two main tasks in portfolio management: resource allocation and product selection as well as prioritization. This chapter aims at deep diving into how the process of portfolio management is structured within a big multinational pharmaceutical company, in particular within Roche. In a multi-business organization such as Roche resource allocation is an exercise performed at the headquarter level, whose decisions are then reverse top-down within the organization’s affiliates. Once Roche makes portfolio decisions on which molecules move forward and prioritize, obviously the ones that have high potential to overcome the hurdles within the development process and being successfully approved by the regulatory authorities, any exercise of product portfolio optimization is country specific and it is therefore run independently at the affiliates level.

3.3.1 Resource Allocation

Resource allocation process at Roche, which mainly concern investing and optimizing resource at the R&D level, and product selection is performed at the highest corporate level. In particular, there are various steps in the decision-making process concerning R&D funds allocation and molecules selection, largely guided by the Corporate Executive Committee (CEC) (Figure 69):

Figure 69 R&D Resource Allocation at Roche



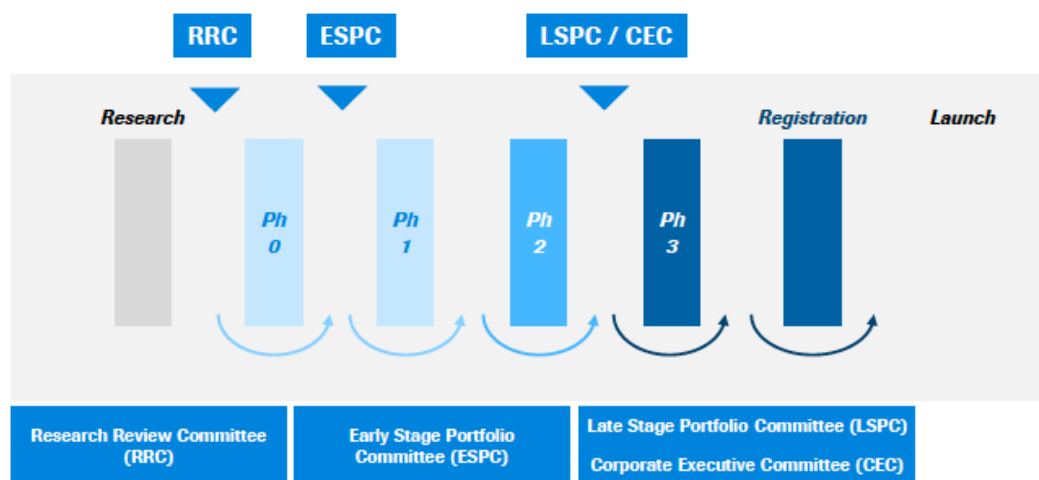
Source: Severin Schwan, Roche Investor Day, 2012

- I. The first step is setting the overall risk appetite for the company. Roche selects how much it wants to spend on R&D overall and given its innovation-based strategy it is clear that it invests over-proportionally compared to the industry level. At the same time given the challenges of the business environment and the inherent risks of the market, Roche commits itself to keep its research and development's spending stable in absolute terms in the medium term.
- II. The following step, typically on an annual basis, involves the definition of the budget for the respective units: diagnostics, research and early stage development (REDs - both pRED and gRED), late stage and the budget for Chugai, as its main partner.
- III. An R&D steering committee, a sub-committee of Corporate Executive Committee (CEC) is then in charge of reviewing the budget allocation for the different disease areas.
- IV. Lastly, three to four times a year *Lifecycle Investment Point (LIP)* transition decisions take place; during these meetings decisions are taken concerning the moving forward of specific medicines to the late stage development and the company's commit to late stage trials.

3.3.2 Product Selection

From the research stage down to the product commercialization stage, different step-gate decision points are identified. Each project is rigorously evaluated at each major independent point with decision-making delegated further down the organization to specific committees (Figure 70).

Figure 70 Major independent stage-gate decision points at Roche

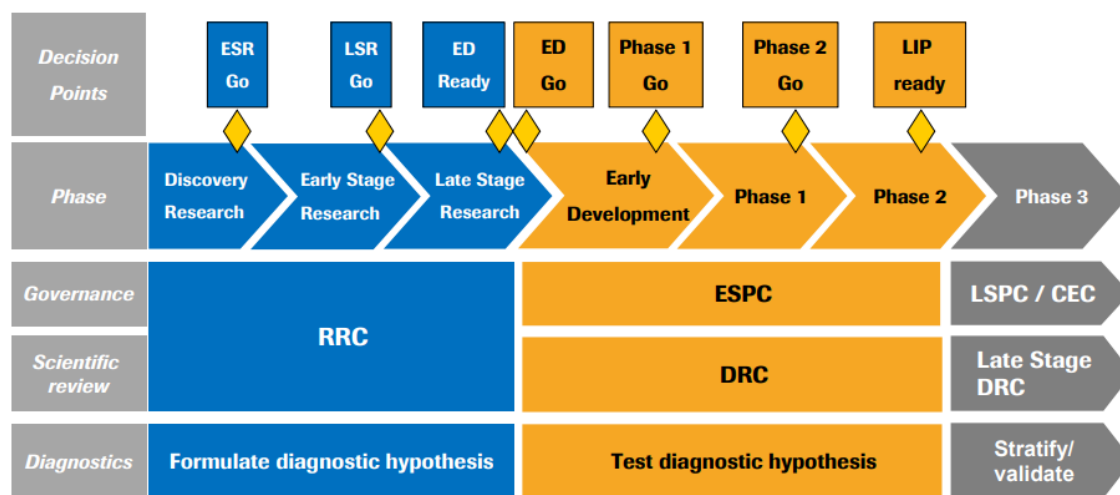


Source: Severin Schwan, Roche Investor Day, 2012

After a molecule is discovered before proceeding with pre-clinical trials the *Research Review Committee (RRC)* decides whether it is worth continuing investigating the new molecule entity. After pre-clinical development, before entering into the early stage development with Phase I and II clinical trials, the *Early Stage Portfolio Committee (ESPC)* is in charge of evaluating the decision. If the molecule yields successful results in phase I and phase II trials, which aim at screening for the drug's safety and establishing its efficacy, then the molecule is said to have proof-of-concept. This is probably the most important decision a pharma company has to make in terms portfolio management. The proof-of-concept is key in moving the molecule forward to late stage development: the challenge in this step is merely deciding how to prioritize investments among the different molecules that successfully passed the phase II depending on their potential to tackle a highly unmet clinical need, their clinical profile and how they fit within the existing product portfolio strategy. The *Late Stage Portfolio Committee (LSPC)*, together with the CEC, is the decision-making body for progression and development of molecules from the Research and Early Development (REDs) organizations, through late-stage clinical trials, filing, approval, launch and post-marketing. The LSPC at Roche sets the performance criteria for early-stage molecules, decides which molecules enter late-stage, and manages development and resourcing of the molecules through their lifecycle throughout all the Roche's affiliates.

If we take the gRED unit as an example, figure 71 illustrates the typical portfolio governance within the Roche group. Genentech’s portfolio governance system is, in fact, actively monitored and managed by the same two committees: the Research Review Committee (RRC) and the Early Stage Portfolio Committee (ESPC), Both these governance committees are constantly making trade-offs on the most promising and innovative projects so that they actively manage a portfolio against their goals of being the first and best in-class. It is important to stress how the decision to move a molecule into late stage development is an independent choice made by the product development unit on the basis of resource-allocation and probability of success trade-offs.

Figure 71 gRED Portfolio Governance



Source: Richard H. Scheller, Investor Day, 2012

This governance structure poses a very high bar on the molecule that successfully moves on into pivotal studies and has served Roche extremely well in the past, putting high pressure on the respective RED hubs to generate convincing data that makes it clear that the probability of technical success in a disease area in which there is an unmet need is high enough to spend financial resources on the molecules. Roche firmly believes on raising the bar and it is keeping the expectations high in terms of next generation medicines by commercially delivering differentiated NMEs. Because of the richness and the receptivity of Roche’s portfolio, prioritization and strategic decision-making during the life cycle management is extremely critical in order to increase productivity and speed up entry into the market. Indeed, because we are talking about medical breakthroughs it is pivotal to continuously improve R&D processes such that internal portfolio management practices across such a large organization do not get in the way of moving these medicines forward quickly. For this reason Roche has created a program named *JEWEL* (Joint Effort to Win b/w Early and Late stage), a fit-for-purpose strategy program to accelerate breakthrough designated molecules and shorten their time-to-market of up two years. Definitely the availability of high-quality real world data and growing expertise in data analytics are fundamental in generating

insights able to improve R&D efficiency as well as access to medicines and creating faster reimbursement on the market place.

Indeed, Roche has always kept the bar very high with a strong filter on medicines that go through late stage development, ensuring that those medicines get access to patient in need. Roche strategy for the long term will continue to focus on highly differentiated medicines and personalized healthcare, with a strong emphasis on pipeline and execution, setting the bar high for new differentiated molecules and making sure that they arrive to patients. At the same time, even though its structure is defined to explore broad multiple numbers of diverse solution to patients' needs, the filter to get to late stage development is significantly rigorous.

“We know that if you bring a marginally differentiated product to the market today, first of all patients aren't going to scream for that, most definitely healthcare system and reimbursement authorities aren't going to find ways to get it to patients. So we set the bar high, we take risks; we don't necessarily meet all the endpoints we expect to meet, but it extremely important to do that: to set the bar high. Because even if we would have set the bar lower and met those endpoints, we would have not have a product that would have met the need of patients.”

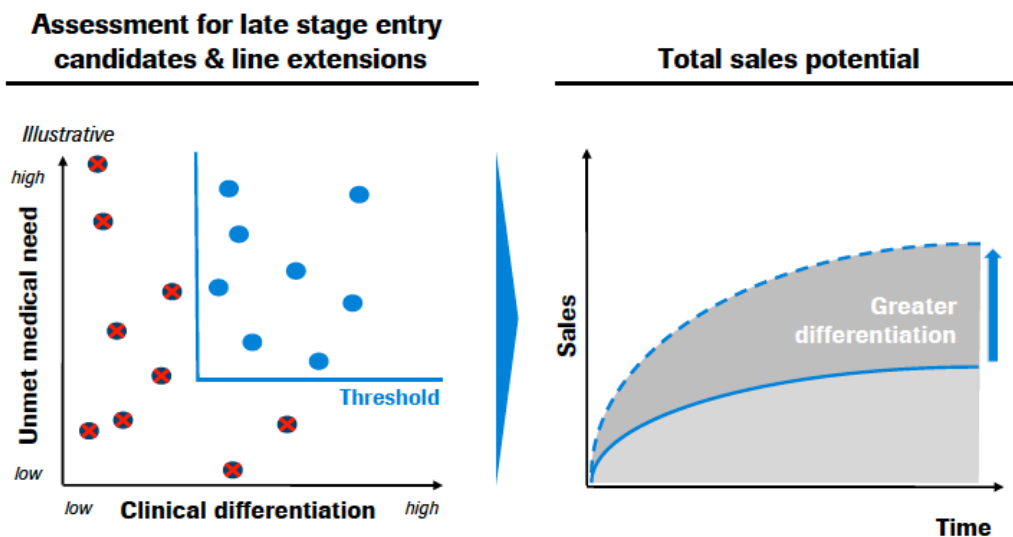
Daniel O'Day, 2015

3.3.2.1 Product Selection: Methodologies in place

Roche set a high bar for its R&D pipeline, to target clear differentiation in areas of unmet need. It has defined a sharply high threshold for the assessment of late stage entry candidates and line extension. The reason behind setting the bar high is because the power of innovation is increasing and also because the threshold of a successful molecule is getting higher: increasing in differentiation leads to greater sales potential and greater return on investment for shareholders (Figure 72).

In order to rigorously prioritize projects within its late stage R&D portfolio and focusing investments on the most promising candidates, Roche relies on different methodologies. One simplified metric used by the Late Stage Portfolio Committee (LSPC) highlights the differentiated approach Roche, as a leading pharma company, uses when deciding on which new molecules coming from pRED, gRED and Chugai organization to accept (Figure 73). On the vertical axis there is the probability of launch (POL) – the success factor – while on the horizontal axis there is the NPV.

Figure 72 Rigorous Criteria to Enter into Late-Stage

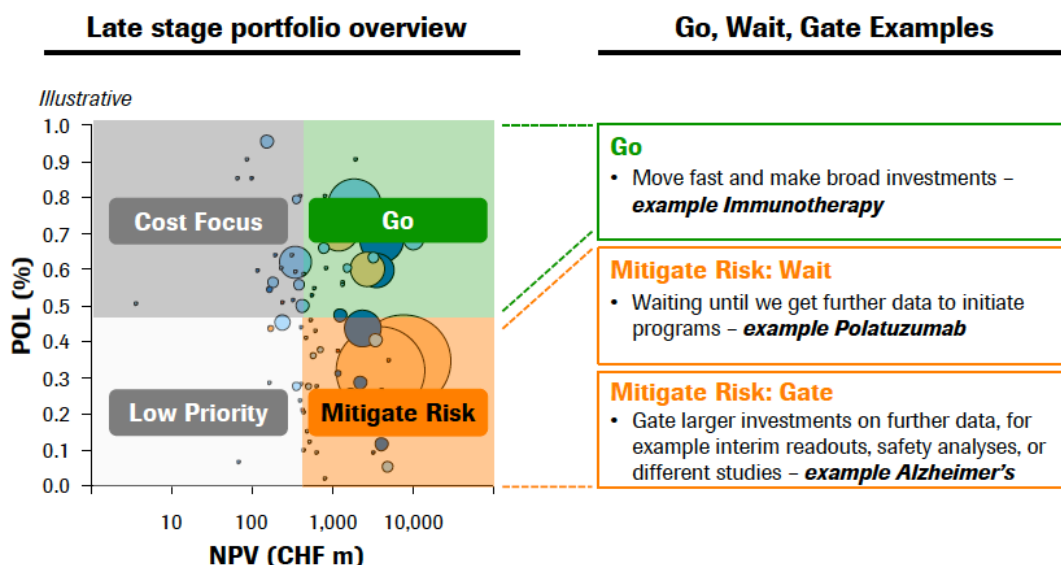


Source: Daniel O'Day, Roche Pharma Day, 2015.

On the upper right corner are displayed the molecules on which the company has good feeling and understanding for either the mechanism or that have witnessed strong Phase I and II data. In this case it's appropriate to take risks to work immediately on the lifecycle management of that molecule to move it molecule as quickly as possible, in advance of even getting the phase III data readouts. The other molecules that fall into the category of high medical need, very high return potential, but maybe more risk and here it is pursued a more mitigate approach. In some cases it may be more prudent to wait for phase III results or on the contrary in other instances appropriate gates will put in place relative to the ability to obtain a differentiated medicine or relative to safety and efficacy. Even though it may look simplistic, it is anything but.

When selecting late-stage molecule to move forward within the pipeline, financial analysis is also performed in order to monitor R&D productivity and value creation, keeping the portfolio balanced from a financial point of view, between the soon to be launched products as well as the ones already marketed.

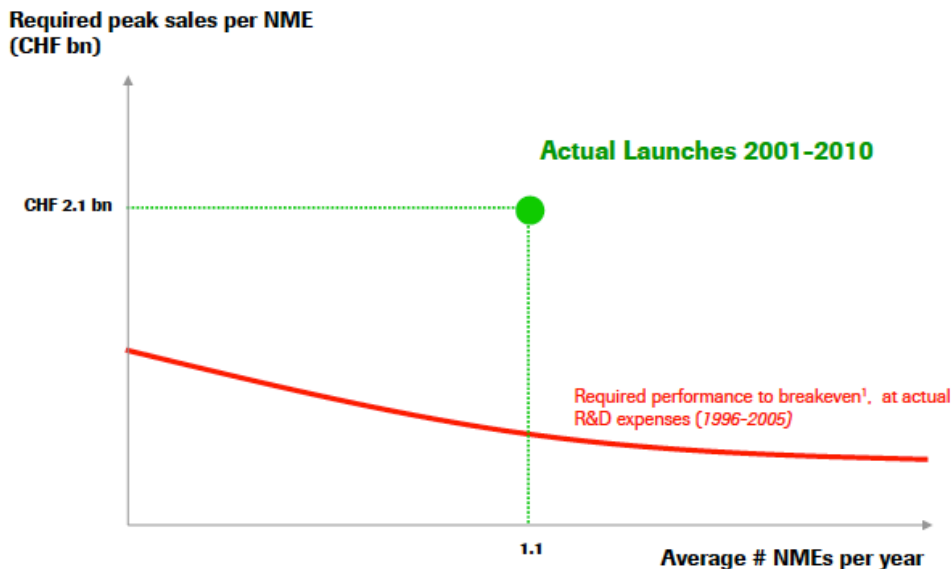
Figure 73 Illustrative Portfolio Matrixes for Late Stage Selection



Source: Daniel O'Day, Roche Pharma Day, 2015.

The graph below (Figure 74) displays the *efficiency line* – the performance required to breakeven – obtained from the combination of NMEs launched in a year, including line extensions, and peak sales, in actual figures. Whenever a firm is above the line it creates value, on the contrary below that the line it destroys it. The projection of the model over the time frame from 2001-2010 for Roche indicates that it was very successful in delivering value creation. Yet this picture represents the past and does not depicts the more recent R&D return enjoyed by Roche. In fact, the increasing R&D spending and costs together with increasing cost of capital has shifted up the efficiency line, which implies that Roche will be under pressure in the future to come up with a higher combination of peak sales per NMEs that it did in the past. The model must be constantly and dynamically matched with the firm's projected pipeline, adjusting it at every success or failure scenarios that may affect R&D productivity to avoid the risks of falling below the efficiency line. This is how Roche monitors value creation coming from its R&D pipeline, making sure it will always be able to deliver value to its stakeholders in the future.

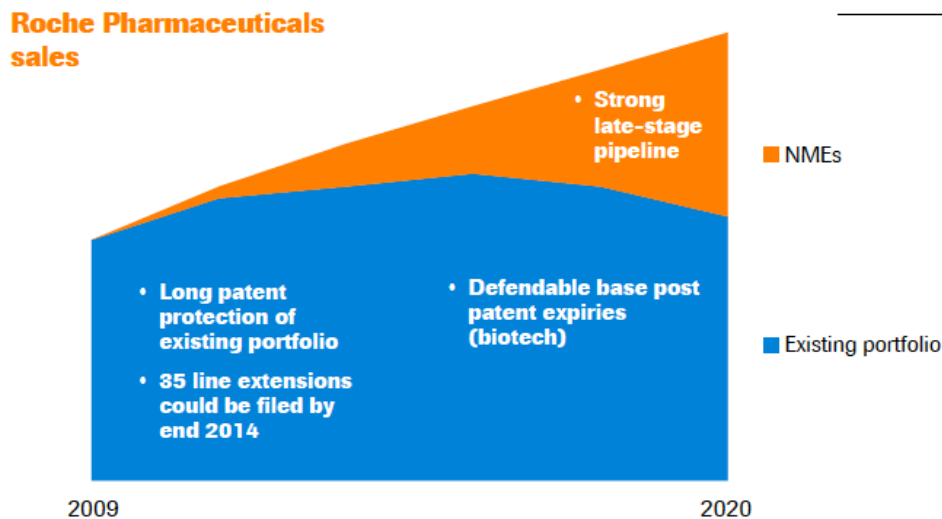
Figure 74 Roche R&D Return, 2001-2010



Source: Alan Hippe, Roche Investor Day, 2012

The point of practising this type of efficiency exercise constantly is to monitor how the forecasted sales coming from both from optimizing the existing portfolio as well as capitalizing on the late-stage portfolio will advance through years, also in light of the evolving market dynamics is critical. Indeed a pharmaceutical company relies on its pipeline as a future stream of cash, while in the mean time keeping maximizing its existing patent-protected products, incrementing sales filing for new indications (Figure 75).

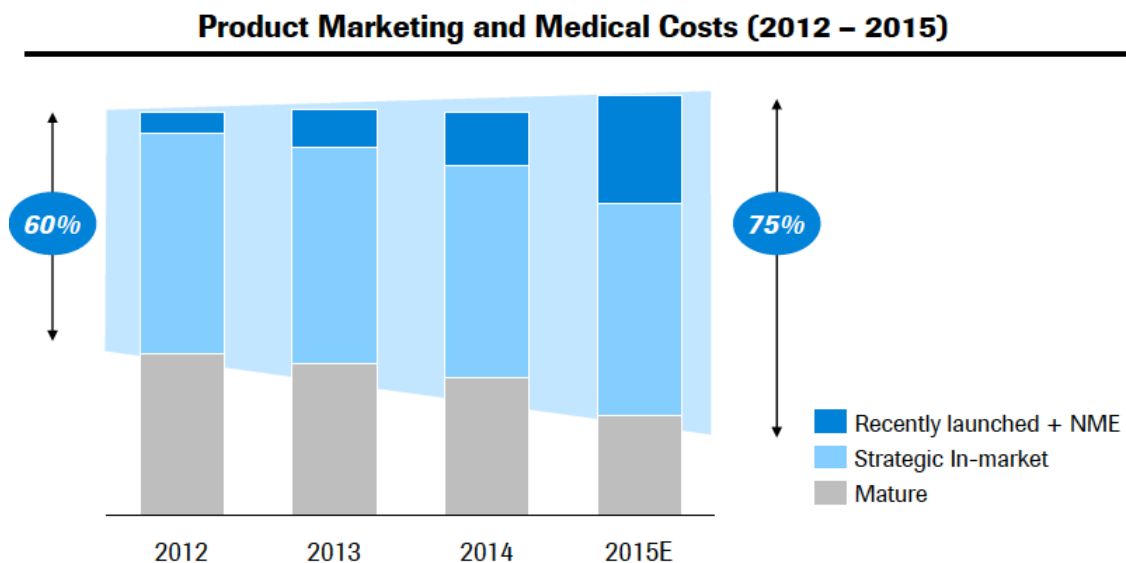
Figure 75 Roche Forecasted Sales from managing existing portfolio and new NMEs



Source: Alan Hippe, Roche Investor Day, 2012

As of today, Roche portfolio is roughly evenly split between oncology and non-oncology assets and 60% of its pharmaceutical products have a companion diagnostic approach, which is not only good for increasing the probability of success but also for the medicine’s reimbursement and access. A clinical differentiated portfolio is only as good as being able to get these medicines successfully to patients. This is why Roche is trying to put great attention to its upcoming launches in order to guarantee broad access to medicines. Through some its non-oncology assets Roche will be entering in the coming years in highly competitive therapeutic areas (e.g. Roche with the launch of Ocrelizumab will be the 13th brand entering in MS) and launching clearly differentiated medicines in in competitive market requires adequate funding; If on the one hand Roche can capitalize on the already developed expertise and capabilities in specialty areas outside oncology, on the other hand it must invest appropriately to make those launches successful. It must be determined what are the resources needed to invest on the medical side, on the marketing side and on the access side to ensure that when these products will be launched, the clinical evidence is understood by all the stakeholders. At the same time a firm aims at efficiency when talking about investment and this is what Roche has started to do since few years ago: shifting investment to new strategic products from mature product that currently still drive its growth, investing significantly on the recently launched while preparing for the coming NME that will come to the market while slightly increasing the overall spending (Figure 76). On the efficiency side, Roche has doubled the number of projects in its late stage development portfolio almost at a flat span without incurring in additional costs.

Figure 76 Roche Costs Evolution



Source: Daniel O’Day, Roche Pharma Day, 2015.

3.3.3 Portfolio Product Optimization at the Affiliate level

In the Italian Roche affiliate, as well as in all other countries affiliate, a specific framework for portfolio prioritization (Figure 77) is being used to lead informed discussion on how to optimize local investment decisions. In particular, the key benefit of implementing such framework in local teams is to rely on a consistent and robust approach for investment decision-making, triggering and focusing the local management's dialogue on the right questions. The outcome of this framework should also consider the downstream implications of investments decision on the change of investment mix for each product as well as the actions to undertake to execute and support new channel mix.

Figure 77 Affiliate's Portfolio Prioritization Framework



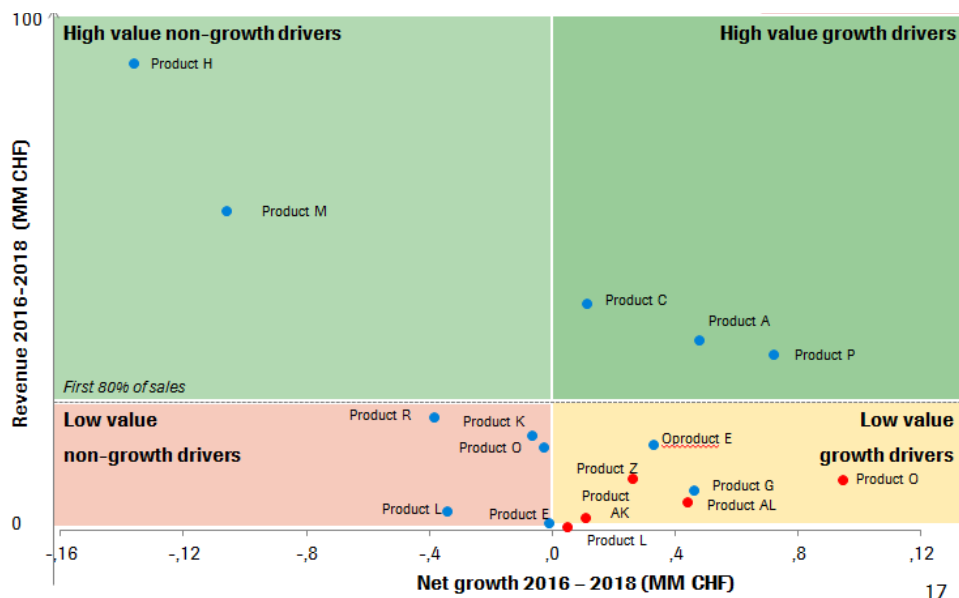
Source: Roche Internal Data

The portfolio prioritization framework thus includes four key steps:

1. **Prioritize:** understand portfolio priorities based on product or indication' sales and growth as well as other additional key parameters. Roche adopts a matrix in which each product within the portfolio is displayed on the basis of current sales importance, future growth and investment sensitivity. The graph locates products in one of the four quadrant on the basis of the combination between cumulative net sales and net sales growth (Figure 78-79): therefore products that fall in the left side quadrants should fund all new launches while those that will drive future growth are place on the upper right side quadrant. Furthermore, the matrix classifies products also according to their sensitivity investment, calculated by weighting treatment duration, competitive intensity, competitive advantage and product growth. The matrix recognizes the growth and value drivers for the affiliate by depicting which products

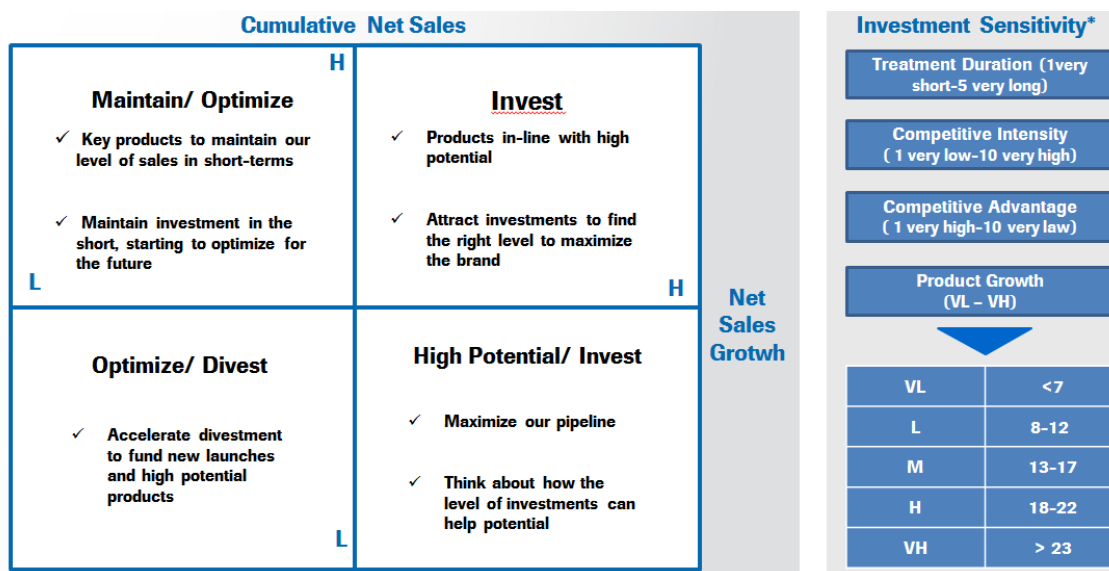
have high value potential in terms of expected revenue and have positive net growth such to be considered growth drivers. The chart has multiple objectives: first and foremost to realize which products represent the short and medium term priorities, at the same time promptly recognizing which product can be deprioritized as well as to comprehend which key parameter can be leveraged to increase sales and growth.

Figure 78 Prioritization Chart



Source: Roche Internal Data

Figure 79 Prioritization Matrix



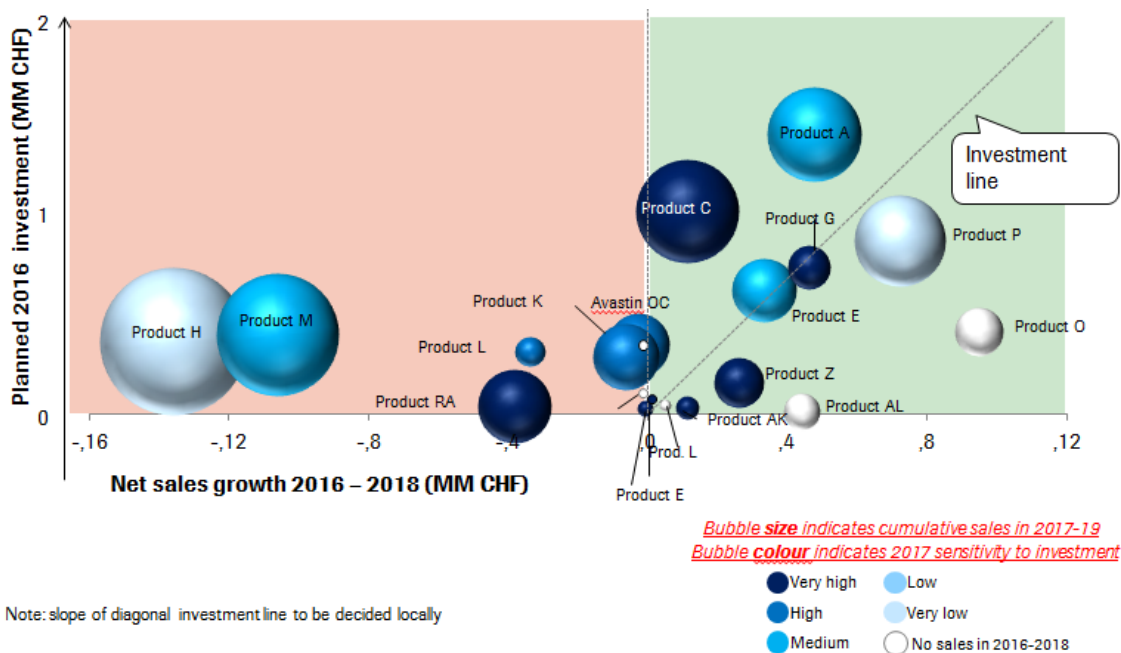
Source: Roche Internal Data

When making informed decisions on portfolio priorities, additional parameters must be taken into account, such as the *competitive intensity*¹⁶¹ and evolution of the market in which each product operates, its *competitive differentiation*¹⁶² on the basis of a qualitative assessment on the strength of the product value proposition with respect to its competitors, as well as an assessment of the *strategic importance*¹⁶³ of the product based on its fit with Roche's strategy. In particular, the prioritization matrix should give insights also on new launches' opportunities by analyzing the impact of different pricing and reimbursement timing scenarios.

2. **Compare:** Balance the planned investment level with growth and value opportunity.

Namely the key questions this step aims at answering concern whether the planned investments for the current year are in line with the short-term expected sales growth (Figure 80). Furthermore through the investment sensibility analysis is pivotal to understand whether growth drivers are adequately resourced in light of their current value and future potential in order to avoid to be either over-or-under-resourced.

Figure 80 Investment Sensitivity Analyses



Source: Roche Internal Data

¹⁶¹ It is measured for every year qualitative, by assessing the competitive landscape (High, Medium, Low) and quantitative assigning a number from 1 to 10 in order to calculate a weighted average.

¹⁶² It answers to the question: To what extent is the competitor eligible patient pool overlapping with ours? It is measured qualitative (High, Medium, Low) and then quantitatively.

¹⁶³ How much does the brand fit with our Roche strategy? What is brand's strategic importance? It is assessed qualitatively (H, M, L) on the basis of different criteria.

There are different methods that can be implemented to assess the investment sensitivity depending on the need for data requirement. A core approach for all countries is generally more qualitative-oriented based on weighting different benchmarks (e.g. treatment duration, competitive intensity, competitive advantage, product growth for the next 3 years).

As any consultancy matrix that was outlined in the previous chapter, also this graph suggests different strategies to implement for products according to their level of net sales growth in and their position with respect to the investment line:

- **Positive** net sales growth and **above** the investment line: optimize investment to support growth by decreasing investments.
- **Positive** net sales growth and **below** the investment line: optimize investment to support growth, exploring opportunities for investment increase.
- **Negative** net sales growth and **above** the investment line: optimize investment to preserve business opportunity.

When comparing products' investments to their value opportunities, it becomes necessary also to have a summary view of sales, growth and investment plans for each product and indication in order to understand whether short-term value generation, growth potential and investment levels align for each brand (Figure 81).

Figure 81 Overall Assessments to Trigger Discussion

Growth drivers	Value drivers	Revenue growth/investment
<i>Net sales growth 2015-2018</i>	<i>Cumulative sales 2016-2018</i>	<i>Absolute sales growth 2016-2018 over planned 2016 investment</i>
Product P	Product H	Product Z
Product A	Product m	Product P
Product Z	Product Z	Product G
Product E	Product A	Product E
Product C	Product K	Product A
Product E	Product RA	Product C
Product O	Product K	Product O
Product K	Product E	Product K
Product L	Product O	Product E
Product MA	Product G	Product M
Product M	Product L	Product H
Product H	Product E	Product RA

Green = generate first 80% of positive growth; Yellow = generate last 20% of positive growth; red = generate negative growth

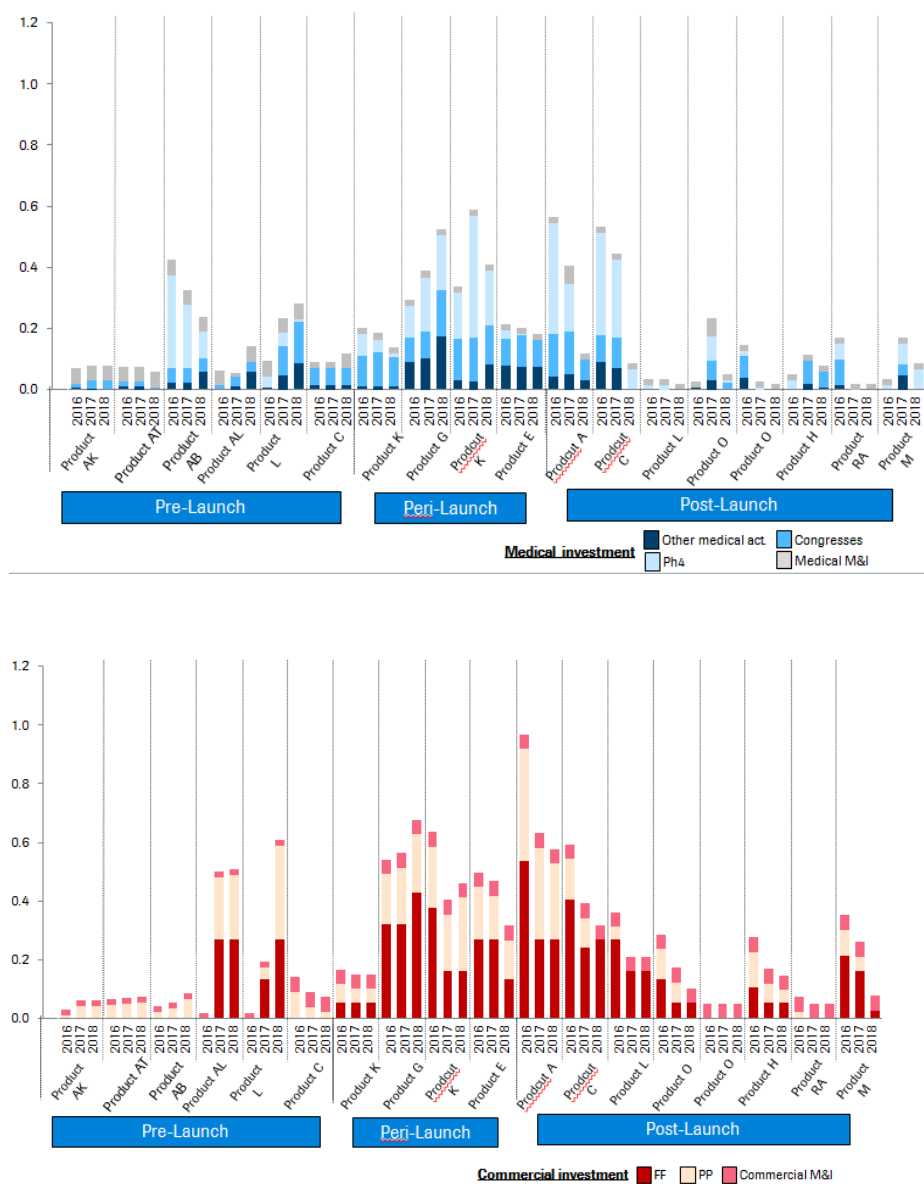
Green = generate first 80% of total 2016-18 sales, yellow = generates next 10% of parameter, red = generate last 10% of parameter

Green = >600%, yellow = between 0 and 600 %, red = negative

Source: Roche Internal Data

- Invest:** Establish investment level for launching successfully. A 3-year resourcing plan and an analysis of the investment mix, both for medical and commercial, and their level across the product lifecycle are important to determine investment needs (Figure 82). Having a clear display of how product investments are spread across the lifecycle stages is useful to assess whether the level/mix of investment is adequate based on the product lifecycle as well as to identify opportunities for investment re-allocation.

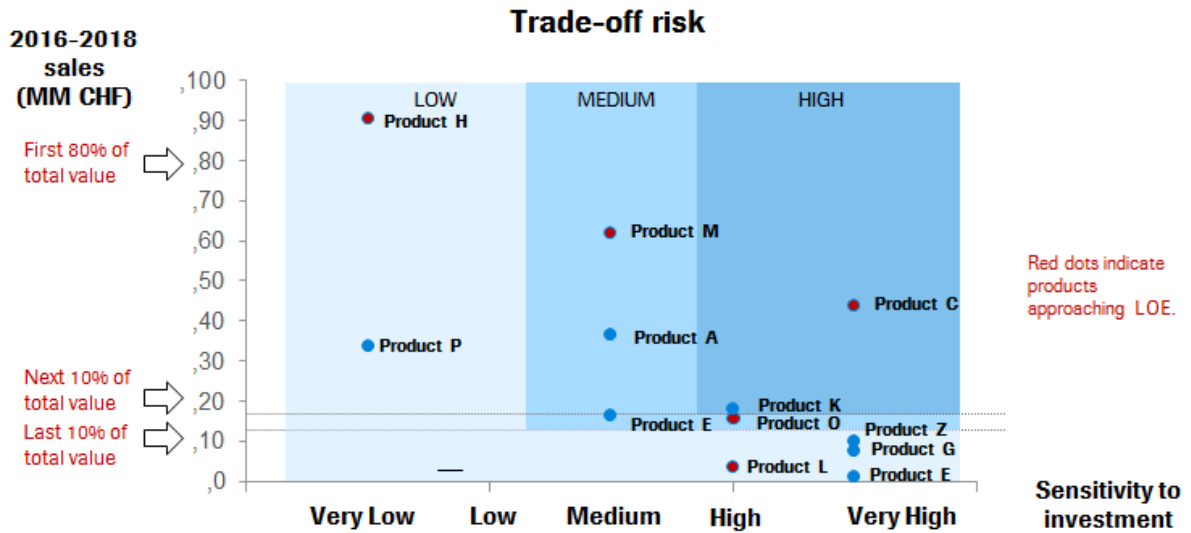
Figure 82 Planned Medical and Commercial Investments throughout the Product Lifecycle



Source: Roche Internal Data

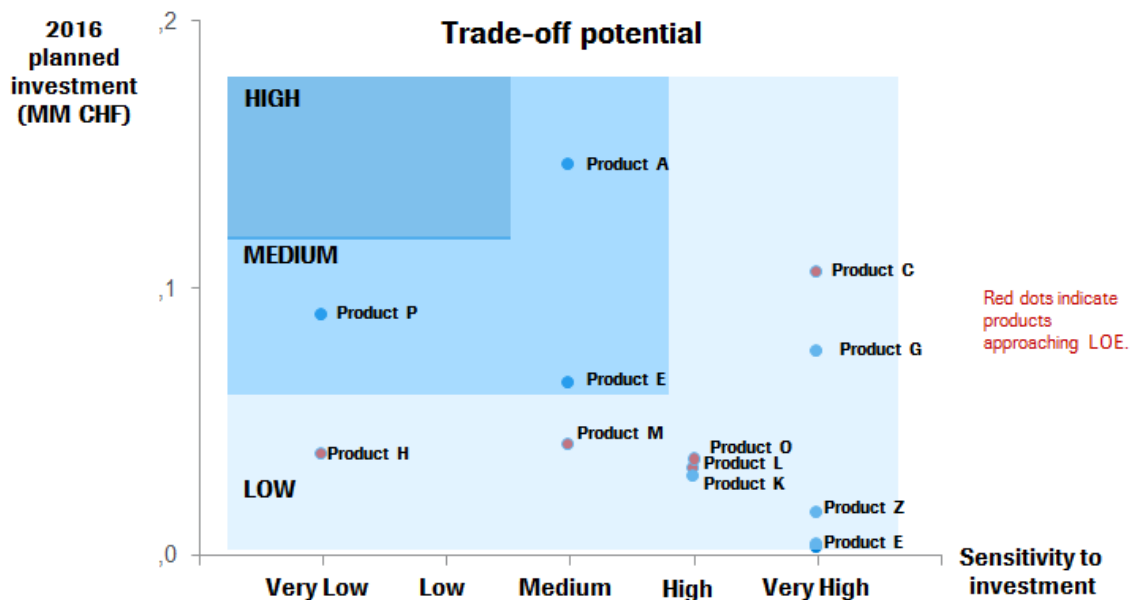
4. **Trade-off:** determine the necessary investment trade-offs for risk-potential. Analysis are performed to judge the sensitivity to investment both to the 3-years sales forecast as well as to the planned investment in order to assess whether there are opportunities to optimize some products or even maintain business results rebalancing investments (Figure 83-84).

Figure 83 Risk Trade-off Analyses



Source: Roche Internal Data

Figure 84 Potential Trade-off Analyses



Source: Roche Internal Data

3.4 Look at the future: Biosimilars' Threat

As previously highlighted, the main challenges Roche will face in the coming years are biosimilars. FDA defines biosimilars as: “A biological product that is highly similar to a US licensed reference biological product notwithstanding minor differences in inactive components and for which there are no clinically meaningful differences in terms of safety, purity and potency of the product” (FDA, 2017). The introduction of biosimilars in the established as well as in emerging markets is an extremely important tool to encourage competition, especially in light of the high costs associated to the existing branded drugs, that can reduce expenses while increasing access to medicines. Indeed, biologics are among the highest-cost treatments available on the market and the price offered by biosimilars are drastically cheaper than their patented counterparts; Thus representing a lower-cost alternative, which is not only attractive but also indispensable in economies where expensive treatments are not financially feasible.

Among other drivers for the introduction of biosimilars to the market, beside the potential for a lower cost alternative, there is the possibility to improve healthcare access while at the same time stimulating competition and thus contributing to the financial sustainability of the overall healthcare system. Nevertheless, despite the incredible advantages, there have several regulatory uncertainties related to the demonstration of interchangeability and automatic substitution between the originator drug and the biosimilar.

Biosimilars are indeed the “hot topic” nowadays in the pharmaceutical world: their undertaking in the EU market can be viewed both as a threat or an opportunity and may drive (and has already driven) changes in many companies' strategic responses. Obviously as of today, no one knows exactly which strategy, undertaken by the lead players, will reveal to be the winning strategy. Nevertheless, it can be interesting to highlight some of the plausible strategic responses to biosimilars pharma companies can undertake, while pointing out what pathway has Roche embarked on in line with its business strategy and long term objectives.

Roche position towards biosimilars so far is quite clear and its position is stated in the media release reviewed in 2016: “Roche is committed to meet high ethical standards in all its undertakings and to sustain and defend the trust of doctors who prescribe and patients who rely on the quality, safety and efficacy of our products. While Roche respects the legitimate undertakings of its competitors, including biosimilar manufacturers, we expect that our competitors comply with applicable laws and regulations” (Media Release, 2016, p.1).

Strategic responses any pharmaceutical firm can employ can either be short term answers or on the other can take longer times to set up and have thus an extended impact on the overall corporate strategy. Among the short term responses a firm can pull out there are:

- *Differentiation* through a better safety and efficacy profile or by providing services beyond the pill to retain the patients' pool.
- *Lobbying* for the development of a well-defined regulatory framework in line with the firm interests in order to avoid automatic substitution with the biosimilar.
- Offering a *competitive pricing* and an aggressive contracting in order to create a sort of oligopoly market.

On the other side of the coin there are all long-term strategic options: first and foremost the need for innovation by investing in internal R&D and developing new products to commercialize. Indeed, for pharmaceutical companies R&D is the main "asset" to create and maintain competitive advantage in the future. Indeed this has been and still is Roche strategy, holding in pipeline numerous NMEs with 20 years of patent protection ahead and 12 new potential blockbusters (e.g Ocrelizumab in multiple sclerosis). An alternative could also be developing commercial strategies aimed at extending a product lifecycle, for example by improving the dosage regimens, investing in a reformulated version or finding complements to existing products. For example the switch to a simplified dosage from IV to SC as it has been the case for Roche's Rituximab or Herceptin can lead to sales increase and a delay in competition. Even though the introduction of a redesigned product, an improved version of the originator drug, has its investments in clinical trials, it has lower R&D costs and higher eligibility for patent protection. Develop products along the same therapeutic algorithm that can function as complement to an existing marketed product can be helpful in postponing competition.

A further strategic option is the possibility to internalize external R&D through M&A or strategic alliances. M&A, as a matter of fact, must not be performed to be the only large company in the market, but rather to maintain leadership position. Acquisitions should go "deep, not broad" aimed at fueling the core business and areas of strength, by acquiring smaller biotech companies with promising drug concepts in early stages. At the same time, strategic alliances and partnerships are ways to "internalize" external innovation and leverage on the combine knowledge and know-hows. Roche definitely prefers internal growth strategies, without relying too much on M&A activities. Nevertheless, it preserves an active network of partnerships spanning over 150 alliances. One of the most recent example of strategic R&D collaboration for Roche is the one it entered in 2015 with Foundation Medicine (FMI), acquiring a majority stake of 53.6% " with the potential for more than USD 150 million funding by Roche to accelerate FMI's new product development initiatives, optimize treatments for oncology patients, and better design and understand the results of clinical trials based on molecular information,

as well as commercial collaboration agreements aimed at expanding the global sales efforts for FMI's current and future products" (Media Release, 2015, p.1).

"Innovation is at the heart of what we do. For us, this means being open to good ideas, including ones generated outside of Roche. In fact, about one third of our pharmaceutical products were born out of a partnership, usually with a smaller biotech firm or university. We maintain an impressive global partnership network spanning over 240 alliances, underpinned by the targeted acquisition of technologies, active ingredients and expertise. In 2014, we entered into a number of important strategic partnerships. The acquisition of the biotech company InterMune, for example, significantly strengthened our portfolio in the area of respiratory disorders with Esbriet, a treatment for a fatal lung disease."

Christoph Franz, Chairman, 2014

Roche's innovation-based strategy and its focus on areas of highly unmet need, has driven and it will continue to fuel its growth. In light of its corporate strategy, its portfolio strategy emphasises both the attention on growing and optimizing the existing business by improving the current standard of care as well as expanding the business through advanced diagnostics and differentiated medicines, by concentrating in new therapeutic disease areas, outside oncology – its comfort zone.

"We need to continue to grow on our existing business, particular in light of the biosimilars (...) I'm confident through the breadth of our portfolio that we'll continue to grow through biosimilars. (At the same time we need to) expand our business beyond our normal walls today (e.g. Ocrevus and Hemlibra)".

Daniel O'Day, COO, 2017.

Conclusion

The good old days of the pharmaceutical industry are over: market conditions are getting tougher with soaring healthcare bills and more burdensome regulations. As healthcare spending relative to GDP continues to rise and regulatory requirements become more demanding, pharma companies undergo scrutiny with little sign of delivering above-average innovation to compensate for such pressures. If permitting regulatory regimes enabled years of expansion and profitability, more recently regulators are introducing new measures raising the bar for entry, particularly in developed countries, showing little inclination to permit market access, price increases, and follow-on products without proof of substantial incremental clinical benefits.

These factors suggest that the industry is heading toward a world where its profit margins will be substantially lower than they were in the past. Players in the pharma industry are facing constant arising opportunities and challenges: the blockbuster business model – on which they became so dependent on – is showing signs of weakness due to the fact that many blockbuster drugs are scheduled to go off patent and Big Pharma earnings’ are tumbling over patent cliffs. The pharma industry continues to evolve, with potential disruptions affecting all parts of the value chain from R&D to patient care, and Big pharmas are potentially facing a “prisoners’ dilemma” in which they are pressured from markets and stakeholders to evolve their business model. In the meantime companies have prepared for the future by in-licensing a substantial part of their innovative compounds from outside firms, as well as outsourcing activities such as clinical trials and manufacturing.

Big Pharma winners have prospered despite industry-wide trends and the demise of the blockbuster model; nonetheless, the future success of today’s market leaders will be determined by how they will react to these changes. Winning companies, despite the struggle to repeat breakthrough innovations, have built a leadership positions and capabilities relying on external growth strategies, mainly targeted M&As. This climate of change thus has required Big Pharma to choose strategic responses for the long-term success that focus on building a balanced heterogeneous portfolio; in fact, to stay ahead of the competition pharma’s portfolio and R&D pipelines must therefore be well prepared to replace those soon-to-be-lost earnings in order to maintain the industry historically high-growth rates.

Conventional wisdom holds that the industry has consolidated. But on the contrary, it has become more fragmented: the number of companies competing for the profit pool has more than doubled. Over the past 20 years, and especially since 2000, building leadership positions through M&A has become a necessary route to succeed in pharma. Between 1992 and 2012, the Big Pharma companies generated 70% of their cumulative revenue inorganically, largely through M&A. One excellent example is Pfizer: since 2000, Pfizer has largely

filled its commercial pipeline by acquiring the product portfolios of competitors like Warner-Lambert, Pharmacia, Wyeth and King Pharmaceuticals. Recent pharma M&A activity suggests that more companies are pursuing portfolio deals to help them lead within particular therapeutic areas. An example is the 2014 asset swap between Novartis and GlaxoSmithKline (GSK) left both companies with stronger positions in their target markets: Novartis in oncology, GSK in vaccines and consumer health.

In order to carefully maintain a balanced heterogeneous product R&D pipeline and product portfolio Big Pharma companies require efficient capabilities in portfolio management (PM), in particular in capital resource allocation and portfolio prioritization. This dissertation, in fact, has aimed at stressing the importance of putting in place a sound portfolio management process, able to lead to effective strategic decision-making.

R&D portfolio management has been embraced by the pharmaceutical and biotech industries because of the unique characteristics of drug development: Huge investments, long development timelines, extremely high risk, and a large number of products in the pipeline. R&D portfolio management, at its very core, is about selecting which projects should be funded—and how they should be funded—and which should be killed, providing processes and tools that enable organizations to not only highlight the potential blockbusters but also to understand the opportunity costs of continuing to fund projects with poor prospects. Portfolio management's holistic view ensures that funding decisions aren't made solely on the basis of products' potential peak sales but take into account also the added value from a timing (e.g. filling a gap in the early-stage pipeline) or market (e.g. growing a key therapeutic area) perspective. By virtue of implementing a portfolio management process, consistency is enforced and the metrics made more credible. The discussion has outlined the most common standardized approaches, both qualitative and quantitative, employed in portfolio analysis and how a bulletproof portfolio management process should be structured. With increased pressure on R&D performance, sound portfolio management practices and efficient processes are viewed as a competitive advantage by the firms that employ them, where they have become an integral part of strategic planning and management. Given the high-stakes of drug development and how well it lends itself to portfolio management techniques, the role of pharmaceutical portfolio management will only continue to grow.

Roche is a leading value creator, a breakthrough innovator since the day it was established, has brought to market one-of-a-kind medicines. Roche has built its leadership position in oncology and target cancer therapies, also thanks to its strategic alliances with Genentech, Chugai and other 150 partners worldwide. As a leader, Roche has benefited from a privileged access to all stakeholders that allowed it to identify and satisfy unmet patients need. Its products benefit from more expertise and stronger relationships, enabling it to get innovations to market faster and with a higher success rate. Roche's innovation-based strategy and its focus on areas of highly unmet need, has driven and it will continue to fuel its growth despite the recent threat posed from Biosimilars entry. In light of its corporate strategy, its portfolio strategy emphasises the attention on growing and

optimizing the existing business by improving the current standard of care as well as on expanding the business through advanced diagnostics and differentiated medicines, by concentrating in therapeutic disease areas also outside oncology – its comfort zone.

In conclusion, it is fundamental for pharmaceutical companies to strengthen PM decision-process, reallocating capital across businesses away from underperforming R&D assets and mature markets that can no longer sustain big sales forces, while investing in those that will represent future cash cows.

What remains still unknown is whether corporate management will test their level of readiness, be agile enough, to accommodate the industry's fundamental changes. To what extent corporate strategies will accommodate current market opportunities and challenges? How would Big Pharma reconfigure their R&D pipeline adjust their current portfolios of business units and marketed products to adapt to the change?

Winning pharma companies all have to make tough choices about where—and where not—to focus their efforts and investments. While some choices may not immediately popular with the markets and stakeholders, companies needs to make informed portfolio decisions on their competitive R&D strategy in order to emerge as winners in the industry.

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SINTESI

Strategic Management Portfolio:

A Focus on the Bio-Pharmaceutical Sector & Roche

Introduction

The pharmaceutical industry is continuously changing and innovating; over the last decade industry leaders have broadened their portfolios and strengthened their balance sheets in the run up to loss of exclusivity (LoE) of their blockbusters. Indeed, companies in this sector have to navigate in an increasingly volatile environment given by the combination of finite patent life, long drug development cycles with high probabilities of failure at every step, the high costs associated with the development and launch together with the post launch market risks. In this respect the efficient management of strategic products portfolio is the necessary condition for long-term survival, thus playing an pivotal role for every company that aims at maintaining its competitive advantage and increasing value for all its stakeholders. Portfolio management – the dynamic decision process, whereby new product projects are constantly evaluated, selected and prioritized – thus is significant in the decision-making process for allocating resources, because it is guided by principles that maximize value, balance components on a number of different parameters, firm’s financial goals, corporate strategy and risk tolerance profile, assuring that any modification represent a strategic fit as determined by a risk-benefit analysis.

Starting from a comprehensive overview the life science industry and its contribution to national economies and healthcare system, the first chapter aims at defining the playing field in which *Big Pharma* compete, highlighting both the micro and macro environmental factors that shape the industry and impact the value creation process. It then focuses the attention to the pharmaceutical and biotech businesses and explains how recent challenges are transforming the traditional pharma business model and how can be leverage to succeed in the new evolving healthcare landscape. Opportunities and challenges are indeed defining a new business environment, eventually determining the evolution towards what has been defined *Pharma 2020*. In the face of challenges in their business environment pharmaceutical companies are being forced to try and reinvent themselves. Only the firms willing to change their corporate strategies, readapting their current products portfolio by choosing the “best jams” will have long-term success. In fact, the key to long-term success lies in building a balanced heterogeneous portfolio. Pharma companies must constantly keep an eye on their portfolios, allocating the right amount of resources to valuable candidates. Even though the paramount goal is clear, there is no defined path to reach it and the route each company have taken depends exclusively on their individual aims and circumstances.

The second chapter therefore intents to deep dive on common growth strategies that have been employed as external sources of innovation to expand firms’ product portfolios, making sure R&D pipelines are well-prepared to replace blockbusters’ soon-to-be-lost earnings in order to maintain the industry historically high-growth rates. As a response to the current market challenges, Big Pharma have re-evaluated their corporate strategies, engaging in a variety of external growth strategies – such as M&A, strategic alliances and licensing agreements. The chapter aims at highlighting the main rationales as well as analysing the main portfolio deals that have occurred in recent years. As business environment continues to evolve, pressures from the payers continue to increase and the costs and risks to develop innovative drugs continue to surge, companies must pursue the strategic alternatives they deem necessary to increasing their productivity and maintain their leadership positions. While doing this companies need to perform strong portfolio management to improve their product pipelines and target areas where they can discover novel medicines in unmet need therapeutic areas. Thus the chapter aims also at reviewing the commonly used techniques and matrices in terms of portfolio analysis employed to inform firms about their own competitive position suggest strategic options and define priorities in terms of resource allocation among the different products or business. Furthermore, it aims at outline how a bulletproof PM process should be structured and at investigates the importance of having in place a sound portfolio management process, able to lead to effective strategic decision-making in order to carefully maintain a balanced heterogeneous R&D pipeline and product portfolio; whenever the firm’s portfolio is judged unbalanced the firm may either grow capabilities in-house leveraging on its internal R&D to generate the next blockbusters or more frequently rely on external growth strategies to shorten the time-to-market.

The last chapter wants to move the attention on Hoffman-La Roche – a worldwide leading research-focused healthcare group. In particular, the chapter emphasizes its innovation-driven strategy and explains how portfolio management within the pharmaceutical division is managed within such multinational corporation. It analyzes how the resource allocation and compound selection in late-stage development process work at the headquarter level. At the same time it outlines an exercise of product prioritization that periodically takes place within each Group’s affiliate.

In conclusion the thesis directs the reader’s attention to a current business challenge faced by pharmaceutical companies, including Roche: the undertaking of the biosimilars in the EU market and how this threat or opportunity may drive – and has already driven – changes in firms’ strategic portfolios through portfolio deals. With this respect it aims at

underlining strategic responses against biosimilars that pharma companies can undertake, while pointing out what is pathway Roche has embarked on. In line with its business strategy and long-term objectives, Roche's innovation-based strategy with its focus towards areas of highly unmet needs, will continue to fuel its growth. Its portfolio strategy emphasises the attention on optimizing its businesses by improving the current standard of care as well as on expanding the portfolio through differentiated medicines, by concentrating in new therapeutic disease areas, outside its comfort zone – oncology.

1 The Life Sciences Industry

This first chapter aims at introducing the life science industry by describing how it has become a key asset for national economies as well as society at large. It will focus on the bio-pharmaceutical sector, emphasizing the dynamics that characterize it, while highlighting opportunities, threats and critical success factors.

1.2 The Healthcare Industry: an Overview.

The pharmaceutical industry is defined as the business of developing, manufacturing, marketing and selling drugs. It differentiates itself by a high degree of complexity; by extend risks associated in particular to the core business activity, R&D, by the need to achieve high economies of scale and scope in order to absorb the R&D costs and by the remarkable margins to be earned. Nevertheless, firms within this sector are subjected to strict regulation concerning patents, clinical trials and promotion as well as control on the pharmaceuticals' efficacy and safety¹⁶⁴. Despite its complexity, this sector is a critical pillar for the economy and represents a vital part of a broader dynamic ecosystem with a high impact multiplier: by providing capital investments it supports demand for innovation through R&D, it generates opportunities and it stimulates many intertwined supply chain activities, such that each gain and loss can have an outsized effect on the economy as a whole. The biopharmaceutical industry, in fact, makes a significant contribution to the European economy, first and foremost in terms of employment.

1.1.3 The Industry in Numbers

The overall global industry¹⁶⁵ has experienced a fairly strong growth over the period 2007-2011, reaching total revenues equal to \$1,107 billion in 2011 thus exhibiting a compound annual growth rate (CAGR) of 6.7% between the same period¹⁶⁶. In 2015 the world pharmaceutical market was worth approximately €715,9 billion at ex-factory price¹⁶⁷. If those sales are breakdown by geographic area it can be noticed how USA and Canada continue to have world's largest share at 48.7%, followed by Europe and Japan. EvaluatePharma (2016) estimates that the prescription drugs sales are forecasted to grow at 6.3% per year (CAGR) reaching \$1.12 trillion in 2022. The core engine behind this growing trend is the new wave of innovative treatments approved by regulators in the last years, especially in the context of orphan drugs. This demonstrates how R&D activities are more oriented towards narrower patients populations characterized by large unmet need and easier market access. Nevertheless, even though the outlook towards 2020 does seem promising and confirms a positive growing trend the pharma industry must still be vigilant for sales at risk due to the imminent patent cliff era ahead in which top biologic blockbusters will be challenged by biosimilars.

Global spending will continue to rise, as the pharmerging markets¹⁶⁸ will contribute a greater share of spending driven by an increasing affordability of basic medicines due to rising incomes. As income will continue to rise based on macroeconomic expansion, government-sponsored programs will also continue to foster access to medicines, limiting

¹⁶⁴ Gianfrate F., *Economia del settore farmaceutico*, Il Mulino, 2004.

¹⁶⁵ It comprises of global pharmaceuticals, biotechnology and life science tools and services market.

¹⁶⁶ MarketLine, *Industry Profile: Global Pharmaceuticals, Biotechnology & Life Sciences*, September 2012.

¹⁶⁷ EFPIA, *The Pharmaceutical Industry in Figures: Key Data 2016*, June 2016.

¹⁶⁸ Pharmerging countries are defined as those with >\$1Bn absolute spending growth over 2012-16 and which have GDP per capita of less than \$25,000 at purchasing power parity (PPP). Pharmerging markets include China, Brazil, India, Russia, Mexico, Turkey, Poland, Venezuela, Argentina, Indonesia, South Africa, Thailand, Romania, Egypt, Ukraine, Pakistan and Vietnam.

patients' exposure to costs and encouraging greater use of medicines. PwC also supports this claim and forecasted that sales in 2020 will be mainly attributable to growth markets¹⁶⁹, which will reach approximately 30% of sales - more than doubling the EU5 countries, as these economies are improving access to healthcare and more people will gain access to basic medicines.

Especially during the last few years there has been intense debate around the affordability challenges faced by the healthcare systems, across all Europe, even though there has been an increase healthcare demand. When medicines' spending is put in context, it is observable that this account for less than one fifth of the total healthcare expenditure in Europe¹⁷⁰, on average 15.9% is spent on pharmaceuticals and other medical non-durables while the majority of costs accounting for outpatient care and in-patient care. However, "medicines are often the principal focus of cost containment policies, rather than government understanding an analysis of the entire healthcare spend [...] (but) the reality is that since 2009 spending on medicines in OECD countries has fallen by an average of 1.8% per year" (EPFIA, 2015, p.6). Soaring healthcare costs are a serious hurdle facing all the stakeholders in the industry and healthcare expenditures as a percentage of gross domestic product (GDP) is climbing in every country at every income bracket (Figure 8), even though it's rising ore steeply in mature markets where the industry has historically made most of its money. It does seems like this trend is unsustainable and indeed government are trying to contain costs in this sector, limiting the growing spending to a level they feel appropriate by pressuring stakeholders to share the burden.

1.4 The Pharma Value Chain:

Generally the phases of research and development (R&D), manufacturing, marketing & sales characterize every drug life cycle. All these activities are strictly interconnected and represent an integrated circuit that is necessary to reach the final endpoint: transform the initial investment in a new medicine viable for patients with medical unmet needs. The key strategic capacities are undoubtedly R&D and marketing, while the manufacturing activity, following the significant pressure on margins, has been subject to an improvement in productive efficiency through the rationalization of the number of productive sites and the relocation in geographic area with fiscal advantages. The drug life cycle coincides with the value chain in the pharmaceutical industry and it is increasingly modular, with the Big Pharma being fully integrated companies along all the value chain while specialized players capturing only some of the value by positioning in specific phases. The highly competitive nature of the industry has resulted in biopharmaceutical companies to find new ways to minimize costs and maximize profits. The pharmaceutical industry has learned to economize on functions that were previously performed in-house and now are transferred to external providers. "Many large pharmaceutical companies have divested significant manufacturing and logistics facilities. They do this as they strive to realign strategic priorities, such as to accommodate drugs losing patents or a re-prioritization of where they wish to add value (e.g. exiting a particular therapeutic area). The contract manufacturers have adapted and made use of (these) opportunities provided to them by both small biotech and large pharmaceutical companies" (Rh, 2017, p.5). Cost-efficiencies and rapid time-to-market are crucial factors in the pharmaceutical industry; by outsourcing get access to expertise and know-hows not available in-house at lower costs, spreading the risk of development and have to possibility to focus on their core business.

1.5 Embrace Opportunities and Face Challenges

The best in pharmaceutical industry is yet to come; the very nature of the industry offers endless opportunities to improve the state of the art and to establish new paradigms of drug development and distribution. As it has been stressed so far there are different forces at play that are impacting value creation while challenging the current blockbusters' business model in the pharmaceutical industry. Namely these best and worst of times are defining the business environment and represent the conditions in place that will eventually determine the evolution towards what has been defined *Pharma 2020*. The outlook has never been more promising on one side and more threatening on the other. Indeed, if on the one hand the industry has witnessed a rapidly strengthening scientific foundation paved by an increasing technological developments, a

¹⁶⁹ Growth markets include BRIC countries (Brazil, China, India and Russia) as well as Mexico, Turkey, Poland, Venezuela, Argentina, Indonesia, South Africa, Thailand, Romania, Egypt, Ukraine, Pakistan and Vietnam.

¹⁷⁰ EPFIA, *Annual Report 2015: From innovation to outcomes*, June 2015.

growing demand for medicines¹⁷¹ especially in growth economies where healthcare access is improving, and the removal of impediments to free trade, on the other hand pharma is facing some enormous obstacles: market condition are getting tougher with Big Pharma's earnings tumbling over patent cliff, harsher price policies and soaring healthcare bills; innovation productivity is declining and regulations are becoming more burdensome¹⁷².

Challenges can be overcome and turned into new business opportunities according to Arthur D. Little (2016), which suggests five key recommendations – key levers – to shape the industry's future and have success in the new evolving healthcare landscape. These key recommendations highlight what have been identified in this chapter the key success factors (KSFs) of the industry: **strong scientific base** paired with efficient R&D, **penetration of pharmerging markets** capitalizing on increasing demand and **value creation through capital investment** strategies.

Constant cutting-edge innovation is key if pharmaceutical companies want to preserve their competitive advantage in the market. Striking win-win partnerships in the industry is one way to identify rewarding prospects and pursue them so that mutual benefits are possible for all stakeholders. Besides betting on innovation, pharmaceutical companies need an efficient R&D system through the implementation of information systems and predictive models and therefore greater technology integration. Many of the top players of the industry have reorganized their R&D model to achieve stronger growth and earnings potential. In fact, following the patent cliff turmoil, organizational structures that worked in the past were no longer sufficient. Emerging markets are tomorrow's source of revenues and the development of those regions makes them incredibly attractive. These countries show relatively low-income levels and growing health problems, which make the market favourable to generic pharmaceutical companies. Companies worldwide are starting to realize the full potential of capitalizing on global expansion, BRIC markets continue to grow and both productions as well as competition levels will continue to rise. Recent trends have led pharmaceutical companies to diversify their product portfolios. During the last decade M&A and divestitures were among the most utilized strategies – and still are – to unlock fundamental changes in order to offset patent cliff, to strengthen key therapeutic areas, to increase market share in emerging markets as well as accelerate the race to develop new drugs expanding products lines and gaining competitive advantage.

Nowadays the pharmaceutical industry is in a period of transition, out of the blockbusters business model typical of the '90s, towards a new strategy for growth in an increasingly globalized market¹⁷³. The empire building strategy utilized by management executives a decade ago has now been replaced by a new business model focused on balancing risk and opportunity through diversification. The slowing pace of drug discovery together with an intensified regulation has increased the urgency of adding new lines of business, in this context increasing reliance on partnerships, acquisitions and joint ventures has proved so far to be an effective method of funding R&D¹⁷⁴.

1.5.1 How to Face Challenges Ahead

The pharmaceutical industry and in particular the so called *Big Pharma* are now experiencing the same phenomenon other industries before them have already faced: being forced to try and reinvent themselves in the face of challenges in their business environment. Only the firms willing to change their strategies and readapt their current products portfolio, choosing the “best jams”, will have long-term success. Companies have responded to these challenges engaging in a variety of corporate strategies – M&A, partnerships, diversification, licensing agreements just to name a few – aimed at paving the way for future success. Mergers and acquisitions in particular are part of these changes: Merck's merger with Shering Plough, Pfizer buyout of Wyeth and Roche's acquisition of Genentech are just few examples of how M&A has been employed for consolidation. Johnson & Johnson, Novartis and Abbot have preferred to follow the path of diversification in other business areas while other players instead have focused strongly on expanding operations in emerging markets through strategic alliances.

In this climate of change the key to long-term success lies in building a **balanced heterogeneous portfolio**. Just like a responsible investment manager does not bet all its clients' money only on risky assets, that only might deliver a big return, but it combines speculative investments with bread-and-butter stocks to generate a steady return, so must pharma companies

¹⁷¹ See par. 1.1.3, The industry in numbers.

¹⁷² PwC, *From vision to decision: Pharma 2020*, 2012.

¹⁷³ Baum A., *New Product Generation and an Easing Regulatory Environment in Biopharmaceuticals*. Wall Street Transcript, Vol. 192(3), pp. 57-61, 2013.

¹⁷⁴ Baldi, F., Baglieri, D., Corea, F., *Balancing Risk and Learning Opportunities in Corporate Venture Capital Investments: Evidence from the Biopharmaceutical Industry*, Entrepreneurship Research Journal, Vol.5(3), pp.221-250, 2015.

constantly keep an eye on their portfolios, allocating the right amount of resources to valuable candidates while also reducing waste from R&D costs. Even though the paramount goal is clear, there is no defined path to reach it and the route each company might take will depend exclusively on their individual aims and circumstances.

2 Corporate Growth Strategies & Portfolio Management

This chapter wants to give an overview at the ways in which companies have tried to modify their ways of doing business and have responded to past changes, in particular focusing on strategic options such as M&A, strategic alliances and licensing. Due to the fact that companies in this sector have to navigate in an increasingly volatile environment the management of a portfolio of strategic products is a necessary condition for long-term survival, thus playing a pivotal role for every company that aims at maintaining its competitive advantage and increasing shareholders value. In this respect, this chapter aims also at reviewing the commonly used techniques and matrices in terms of portfolio analysis, both for already marketed products as well as those still in pipeline, employed to inform firms about their own competitive position, suggest strategic options and define priorities in terms of resource allocation among the different products or business.

2.1 Corporate Strategies in the Biopharmaceutical Industry

Corporate strategies put in place by companies, independently from the industry-type and the mere rationales – whether they aim at either horizontally or vertically expanding or diversifying the business – can fall into two options: *internal* or *external* growth. The former assumes that growth is based on the efforts and resources internally from the firm. Organic growth strategies are common in new product development, product-related strategies and also international expansion. The latter instead – also defined as inorganic growth – implies that growth is achieved by looking outside the firm itself, relying on relationships with third parties. Relationships can take different shades – from M&A to strategic alliance and JV, from licensing to venturing – each one has its own pros and cons and it is pursued according to the goals firms’ intent to achieve. It is generally acknowledged that growth should be fostered first and foremost with internal resources and only when these investments become economically unsustainable must then firms examine opportunities outside. Pharmaceutical companies have in the last decade preferred to look outside to fill the weak in their pipelines and spur growth.

In the midst of challenges pharma companies look at M&A and other form of strategic partnerships as the easy way out to address the problems they face. Especially when companies dispose of substantial cash flows to invest, M&A activity has been the most widely used strategy to hedge against the adverse impact of patent cliffs and the associated expected revenues’ shortfall, as well as to increase competencies and know-hows to trigger R&D growth. As the risk of revenue shortfall increases even companies with solid growth projections may pursue M&A to protect against the downside scenarios. While some companies may focus on defensive M&A, others may prefer alternatively to diversify their revenue mix away from the pharma core business in adjacent life science business areas such as vaccines, animal health or medical devices.

Nowadays industry outlook indicates, yesterday as today, an active biopharma deal environment as a direct consequence of the global industry’s structural shift towards externalizing R&D and in response to the intensified power exhibited by payers. Even in markets such as oncology where companies have relatively strong pricing power, continued growth might become difficult. This is why also divestiture strategies have been put in place to shed underperforming or undersized businesses while refocusing on diseases areas where companies can compete for the leadership¹⁷⁵. As Fred Hassan, former CEO of Schering Plough stated in an interview in 2010¹⁷⁶ “large drugmakers will need to merge to fund expensive, complex areas of research such as Alzheimer’s disease. [...] One reason deals are necessary is because innovation investments are becoming larger and larger and it makes it easier when people can combine their resources to

¹⁷⁵ EY, *M&A Outlook and Firepower Report 2017*, 2017.

¹⁷⁶ Pettepiece S., *Former Schering Plough CEO Hassan sees more deals among drug-makers*, Bloomberg, February 2010.

make the big deep bets that you need to make for difficult diseases.” Finding therapeutic “white space” in unmet areas may require companies to pursue higher-risk opportunities, “driv[ing] future M&A as companies compete for the best assets in key (...) areas where drug sales currently represent a smaller portion of total related healthcare costs” (EY, 2017, p.3); this win-or-go home mindset is what’s driving today’s M&A and divestiture agendas.

2.2 M&A Strategy:

M&A activity on large scale played a pivotal role in influencing the performance of the Big Pharma over the years in terms of sales’ volumes. From 1995 till 2014 the total sales value realized from the Big Pharma experienced a growth of \$297.4Bn in absolute terms – from approximately \$84Bn to \$381Bn. A MarketLine analysis estimated that such incremental value was to be attributed for 63% to the sale generate thanks to M&A activity. M&A activity has allowed firms to increase in scale, positively influencing the proliferation of successful blockbusters into the market, which consequently led to an upturn in revenues. Indeed, only in the time period between 2001 and 2008 sales revenue generated by major blockbusters increased with a compound annual growth rate of 11.2%¹⁷⁷. If on the one hand these waves of M&A transactions, oriented to acquisition of blockbusters in their pipelines, contributed significantly to the growth of the acquiring firms, on the other hand the pressing need to constantly and successfully update their product portfolios to counterbalance the off-patent risk represent one of the main weaknesses of this strategy¹⁷⁸. In fact, because big pharma’s R&D function cannot always guarantee a portfolio in equilibrium, in order to allow for a constant turnover that it is essential for a company long-term sustainability, M&A remained the easy way out, especially in a decade where pharma’s main business model revolved around blockbusters. Furthermore, M&A activity allowed big pharma companies to internationalize as well as to strengthen their capabilities in terms of sales and marketing.

Nowadays outlook is the age of strategic deal making and “portfolio deals”– selling critical business to better suited players to own and manage them as well as looking for critical portfolios to acquire – and Novartis clearly set the example in the industry in 2015. The multiple swaps between Novartis and GSK and Eli Lilly, which strengthened Novartis’ position in oncology and GSK’s in vaccines while relieving Novartis of its animal health business unit in favor of Eli Lilly. “In a phase where many players [...] still believe that ‘bigger is just better’, more sophisticated companies realize that only a strong position in the relevant market will secure the future” (IMAP, 2016). More than any other time in the past, “big pharma companies have the firepower¹⁷⁹ advantage necessary to execute the acquisitions they require to bolster revenue and drug pipeline. And more than any other time [...], those deals are necessary. Big pharma and biotech’s race for inorganic growth has intensified as payers continue to push back on price increases for older drugs and dampen the growth trajectory of newer therapies, especially in increasingly crowded disease areas” (EY, 2017, p. 2).

2.3 Beyond M&A: A Kaleidoscope of Corporate Strategies

The debate is still ongoing regarding what is the best approach for long-term viability. As Andrew Jack¹⁸⁰ once wrote in article on the FT in 2009¹⁸¹: “rarely in the field of pharmaceuticals have so many companies adopted such varied strategies in order to survive the intensifying structural pressures in their industry”. The problem is that there is not one magic solution guaranteed to work. To compete in such rapidly evolving environment, biopharma companies must be able to assemble the right capabilities and know-hows and to achieve this outcome business development is key. Strong external relationships and partnering are also the secret for building the right portfolio of assets and “collaboration to gain access to early innovation has long been a mainstay for pharmaceutical companies” (J. Orloff, EY interview transcript, 2016, p.60). Given the current market challenges and opportunities, with increasingly high pressures from the payers, the costs and risks

¹⁷⁷ Zoli, Elisa, *Prede e predatori: il ruolo chiave dell’M&A nell’industria delle Big Pharma*. Tesi di Laurea in [Finanza aziendale avanzato](#), LUISS Guido Carli, (A.A. 2009/2010).

¹⁷⁸ An example could be the acquisition of Wyeth by Pfizer in 2009, whose main rationale was reducing the loss and filling the hole left by Lipitor, a blockbuster product for the company responsible for 23% of total sales revenue, going off-patent.

¹⁷⁹ According to EY the Firepower index measures a company’s ability to do M&A based on the strength of its balance sheet. Company’s market capitalization, cash equivalents and debt capacity provide the firepower for deals.

¹⁸⁰ Andrew Jack is multiple award winning journalist, who has been writing for the Financial Times since 1990 and who specialized in health and pharmaceuticals since 2004.

¹⁸¹ A. Jack, *Pharma split on nature of merger as kill or cure*, Financial Times, March 2009.

to develop innovative drugs will continue to surge. It is crucial, therefore for big pharma companies to pursue the most diverse strategic alternatives they deem necessary to increasing their productivity and maintain the historical high growth rates. “As business environment continues to evolve, companies must continue to implement new approaches to improve their product pipelines and look for new patients and markets to serve. While doing this they need to rigorously assess their business, ensuring their strategies are financially sound, perform strong portfolio management to target areas where they can provide novel medicines in unmet need therapeutic areas” (Baines, 2010, p.27).

2.4 Portfolio Management

In the context of corporate strategy the portfolio represent the means through which resources are allocated in order to deliver strategy. As David Matheson defines it, a business portfolio is “a related set of assets that compete for resources and deliver value for an organization”. Portfolio management thus plays a critical role and it is a common business function across all industries, in particular within innovative ones. “Portfolio management creates a dynamic capability to react purposefully to changes in the market [...] and (it) is all about providing a strategic perspective and [...] ensure that resource allocations are in line with corporate strategy, by seeking balance across a range of dimensions” (Arthur D. Little, 2015, p.6). The process includes identifying, prioritizing, managing and controlling projects to achieve specific business objective and when poor portfolio decisions, not aligned with the company’s strategy, are taken these can significantly impact firms’ performance. In the context of the pharmaceutical sector, portfolio management is defined as a set of activities that allow companies to select, develop and later commercialize a pipeline of new products aligned with the corporate strategy, in order to continue to grow profitably over the long-term¹⁸². Within a single pharmaceutical firm the simultaneously development of hundreds products that can cost hundreds of millions of dollars over 5-15 years and fail most of the time, the ability of portfolio management to improve decision-making can have a significant impact on the bottom line¹⁸³. Pharmaceuticals firms have relied on portfolio management to continuously make decisions regarding their pipeline, because of the abundance of project alternatives at every level of the drug discovery and development process, but even after products are launched in the market. Indeed, the impact of rising and falling productivity levels has led pharma firms to pay closer attention to their portfolios and look for established framework and set methodologies to help them balance their portfolio and remain competitive. Indeed as Tiggermann et al. (1998) state the most effective use of portfolio management is not the value calculation, but rather how the information generated are helpful in developing, defining and carrying out the overall business strategy.

2.4.1 Portfolio Analysis

One of the main activity through which corporate management creates value is by effectively managing its overall corporate portfolio, but to guarantee success organizations need to find methods for assessing the balance in their portfolio, which will help them with an optimal allocation of resources¹⁸⁴. Portfolio analysis¹⁸⁵ – the process used in strategic planning to assess a company’s competitive position and business performance relative to its market in order to optimize investments and efficiently allocate resources towards the right business opportunities – therefore represents the conceptual framework that guides and assists management in corporate strategic decision-making¹⁸⁶. Keegan et al. (1992) defined portfolio

¹⁸² Kester et al. (2011), *Exploring Portfolio Decision-Making Processes*. Journal of Product Innovation Management, Vol. 28(5), pp.641-661.

¹⁸³ Smith D., *Why is Portfolio Management So Successful in the Pharmaceutical Industry?* Enrich Consulting, 2014.

¹⁸⁴ Hooley G.J., Saunders J.A., Piercy N.F., (1998). *Marketing Strategy and Competitive Position*, 2nd Edition, Hertfordshire, England: Prentice Hall Europe; West, Ford, Ibrahim (2010). *Strategic Marketing*. 2nd Edition, Oxford University Press.

¹⁸⁵ Portfolio analysis can be discussed from the perspective of business but also from the angle of the single products in a company portfolios. In the discussion that follows this thesis the tools and models taken into consideration can be applied to both business and products are interchangeably.

¹⁸⁶ Fifield, P. (1992). *Marketing Strategy*. Oxford, England: Butterworth Heinemann Ltd; Jain, S.C. (1993). *Marketing planning & strategy* (4th ed.). Cincinnati, Ohio: South-Western Publishing Co.; Aaker, D.A. (1995). *Strategic Management* (4th ed.). New York, NY: John Wiley & Sons Ltd.; Byers, L.L., Rue, L.W., & Zahru, S.A. (1996). *Strategic management*. Chicago, IL: Richard D. Irwin;

analysis as “a way to assess the needs, allocate resources and spread risk across the (business units or products) which contribute to the achievement of corporate objectives”. Some business units may have higher and more attractive growth and profit potential than others and may differ in terms of cash flow characteristics – some are net cash generators, others require to grow in attractive market or will be using cash in declining ones. Either ways this is when portfolio analysis kicks in to “help diversified firms assess the balance of business¹⁸⁷ in its portfolio and guide resource allocation among them [...], allocating strong resources to more profitable businesses – likely its core business – and minimal or no resources into business with less or no margin” (Udo-Imeh et al., 2012, p. 104). Hence, the aim of portfolio analysis include:

4. *Analyze* the current portfolio and decide how to allocate investments.
5. *Develop* growth strategies to add new products into the portfolio to fill the gaps.
6. *Decide* which businesses or products should be divested and no longer be retained.

2.4.1.1 Tools & Models:

Matrices are the most widely used form of strategic tools companies rely on to keep their business portfolio in equilibrium: they provide the necessary information to manage and maintain the portfolio balanced in terms of industry attractiveness and business competitiveness. The discussion that follows reviews four of the main matrices (*BCG*, *McKinsey*, *Arthur D. Little and Shell*) in terms of their characteristics, strategic implications and limitations. . Even though these tools do not provide clear-cut strategic recommendations, they do facilitate the strategic planning process leading to strategies improvements, by summarizing information on the overall company’s market position and giving insights on the balance of the businesses, their relative strengths to competition as well as the opportunities open to them. Exercises of portfolio analysis are not performed to dictate any strategic decisions but they do provide corporate management with the data needed to make informed decisions. Nevertheless their greatest challenge is the implementation at the organizational and operational level because they continue to remain “well-known but underutilized and misunderstood planning tools” (McDonald, 1990, p.11).

2.4.2 R&D Portfolio Management

Conceptually R&D portfolio management falls within the more general area of portfolio management with the same objectives: reviewing the allocation of corporate resources and ensuring that the combination of its project-level activities will allow meeting its strategic objectives. Indeed, portfolio decisions begin first and foremost at the R&D level by balancing the potential delivery of R&D results over time, determining which R&D projects should be funded and at what level. Unfortunately resources are often limited for every company in every sector and a major challenge in portfolio management is “saying no to a good idea to fund a better one and making decisions about project selection [...] prioritization and allocation of resources based on a well-balanced portfolio” (Creswell, Dec. 2011, p.1). For this reason Matheson & Matheson (1997) first introduced the so-called *R&D Grid: Project Portfolio Matrix*¹⁸⁸ aimed at helping companies to understand projects differences and their contributions to the overall portfolio. The grid measures therefore projects in terms of technical difficulties and commercial potential, classifying them in bread and butter, pearls, oysters and white elephant according to each project characteristics. Matheson explains that the grid should help companies to assign to each R&D project an appropriate quadrant based on a quantitative evaluation of its opportunities. Companies should capitalize on pearls, eliminate or reposition white elephant, balance resources between bread and butter and oysters projects to achieve an overall alignment with the corporate strategy. Although projects are defined quantitatively, they are each qualitatively different one another: bread and butter are incremental products or process innovations to generate short-term results; pearls are valuable projects that have the potential to become breakthroughs to be exploited; oysters are defined by uncertainty and it should be quickly determined which oysters contain pearls and which are empty so to avoid spending time on failure. In this context, capitalizing on pearls and discarding white elephant projects represent the easy portfolio

Thompson, A.A., & Strickland, A.J. (1996). *Strategic management: Concepts & cases* (9th ed.). Boston, MA: Irwin McGraw Hill; Kotler, P., & Keller, K.L. (2009). *Marketing management* (12th ed.). Upper Saddle River, NJ: Pearson Prentice-Hall; Kotler, P., & Armstrong, G. (2010). *Principles of marketing* (13th ed.). Upper Saddle River, NJ: Pearson Education.

¹⁸⁷ Hill and Jones (1989) defined a balance portfolio as one that enables a company to achieve growth and profit objectives associated with its corporate strategy without exposing the company to excessive risks.

¹⁸⁸ see note 120.

decisions, the difficult ones concern funding on bread-and-butter and oyster projects; it is by making these difficult choices, between long-term and short-term, that management defines corporate value creation.

2.4.2.1 Financial Valuation Metrics

The pressure on companies to replenish pipelines with innovative drugs that have high potential for approval and reimbursement has driven companies to revise their portfolio strategy over the last decade, allocating R&D budget to projects that maximize the total value of the entire portfolio relying mainly on financial metrics and focusing on individual products' revenues and costs¹⁸⁹. Given these statistics and the unpredictability of the pharma pipeline outcome, managers are driven to make educated guesses on the basis of past experiences of prior success and failures. In order to avoid the consequences of bad outcomes they tend to rely, sometimes even over rely, on standardized financial metrics and criteria that have the potential to pick winners and predict which projects can achieve the higher level of return on investment. As R&D projects selection becomes more challenging, solid financial valuation metrics come into play rather than relying only simply qualitative methods, as in the case of the consultancy firms' matrices outlines above, and strategic decisions are based upon those valuations. This confirms the foundation that a robust R&D portfolio management methodology must be in place to carefully balance the specific R&D project expected value with its expected impact in terms of technical and commercial uncertainties. For this reason firms tend to rely heavily on quantitative modeling methods which present selection decisions as rational evidence-based¹⁹⁰; In fact, according to Smith and Sonnenblick (2013) the success of portfolio management lingers on having a strong portfolio group with access to projects data and their ability to manipulate those data in to concrete what-if questions. Generally the evaluation of those projects that successfully ace phase II clinical trials and obtain proof of concept is grounded on quantitative financial parameters before entering full development. However, firms that rely solely on financial methods for project selection and decision-making perform worse than the other firms according to Kester et al. (2011).

There are several methods that can be used as evaluation tools in pipeline assessment; the challenge is to choose the right number of approaches, since each one in its own ways assesses risk and returns relating to R&D portfolios to aid executive in strategic decision-making. The most standard approaches evaluate portfolios are mathematical frameworks with a value-driven approach, used to determine the optimum size to maximize the value of the portfolio under budgetary constraints: namely, optimizing objective functions given a set of constraints. Portfolio valuation in the pharma sector involves sizing R&D portfolio as a function of expected revenues and making inclusion-exclusion decisions on a compound-by-compound basis¹⁹¹. "Computationally intensive approaches" are usually the best suited to manage the complexity "brought by the projects' dependencies, pipeline resources, and economic and technical uncertainties; each of (the projects) must be managed before a sequence of new product development projects maximizing the expected economic returns at an acceptable level of risk for a given level of resources". The most common methods include: *Discounted cash flow (DCF)*, *Net present value (NPV)*, *Decision tree analysis* and *real options*.

The real value of an organization's portfolio requires a holistic view beyond financial metrics that considers both the business strategy and fit within the organization's business model, as well as it takes in to consideration the views of all stakeholders¹⁹². To obtain the optimum selection and balance in a portfolio, firms must first understand where and how markets will develop over the medium and long term as well as recognize the different stakeholders' requirements, their influence and the weight of their needs such that they can become an integral part of the organization's strategy, which is followed also through to R&D planning¹⁹³.

2.4.3 Portfolio Management Process

¹⁸⁹ Quintiles, *Strategic Portfolio Management & New Influencers in R&D Decision-Making*, White Paper, 2013.

¹⁹⁰ Kester et al. (2011) as cited by Jones (2016)

¹⁹¹ Evans, R., Hinds, S., & Hammock, D. (2009). *Portfolio analysis and R&D decision making*. *Nature Reviews Drug Discovery*, Vol. 8(3), pp.189-190.

¹⁹² It includes the payer, healthcare providers, patients, and patient associations.

¹⁹³ For example, if the firm business model is focused on meeting unmet medical needs, the organization requires a portfolio that ensures a leadership position versus the competition with value demonstrated through improved patient outcomes. If the business is, however, focused in the generic market, a business model based on demonstrating quality and value without compromising patient outcomes must be required.

“In an industry where innovation and time to market are the key determinants of success, the companies who best manage their innovation efforts stand to gain at the expense of their competitors” (Duelli et al., 1998, p.11). When managing a portfolio, indeed, funding decisions are extremely important for establishing long-term growth and making the wrong ones can be devastating for a firm’s budget¹⁹⁴: “deciding on the right portfolio can mean the difference between remaining competitive and falling behind” (Jones, 2016, p.4). For this reason organizations have started to recognize the importance and establish a credible tailored dialogue decision process across their global organization for portfolio management, which should provide “a systematic method for evaluating, prioritizing, and investing in the best research projects, and then driving these projects through the development stage to generate profitable products” (Duelli et al., 1998, p.2). Jones (2016) reports that organizations with an effective portfolio management process in place have 62% of products that meet or exceed return on investment (ROI). Portfolio strategy decisions are therefore made throughout a custom-tailored decision process that varies in terms of requirements from company to company but it is structured in a common way – through individual projects reviews at predetermined stage gates combined with an entire portfolio review – to answer to similar needs in terms of resource allocation and product prioritization. Bode-Greuel and Nickisch (2008) specify that in the pharma industry the portfolio management process entail stage-gate decision checkpoint, related to the major preclinical and clinical development milestones, when progress is measured and it is decided whether the achieved results support the continuation of development or the project should be reprioritized. Decision-making is one of the core functions of any drug development company, essential for determining the firm’s long-term success. In fact, a company’s portfolio can only become successful when supported by the right decisions. Therefore it is imperative that an efficient portfolio management demands effective decision-making. Decisions must be coordinated following a process plan fully integrated with the company strategy, through preplanned decision points and that needs to be constantly updated. Bearing this in mind, Arthur D. Little in an R&D management best-practices case study of 2015, highlights the three sequential steps of to follow for a successful portfolio management process:

1. *Link to Strategy;*
2. *Optimizing the existing portfolio;*
3. *Select new Project.*

3 A Closer Look at Hoffman- la-Roche

3.1 Company Overview

F. Hoffmann-La Roche, or simply Roche, is one of the leading research-focused healthcare groups worldwide. Headquartered in Basel, it is engaged in the discovery, development and commercialization of innovative diagnostic and therapeutic products. Roche is one of the world’s largest biotech companies, with 17 biopharmaceuticals on the market and a large and diverse portfolio of biopharmaceuticals in pipeline, compared to the industry average. The group can count on several truly differentiated marketed products in five main therapeutic areas: oncology, immunology, ophthalmology, infectious diseases and neuroscience. Oncology is by far the largest therapeutic areas in which Roche operates, generating approximately 60% of its sales in 2014. Over the years Roche has developed and commercialized numerous molecules that have contributed to improve patients’ overall survival as well as their quality of life. Still today, six out of the ten top-selling Roche’s pharma medicines, in terms of global sales generated in 2016, belonged indeed to the oncology business. Roche keeps its Pharmaceuticals and Diagnostics divisions¹⁹⁵ under the same roof, which both operates on the most cutting-edge frontiers in order to continuously contribute to healthcare improvements, making Roche ideally positioned to drive personalized healthcare forward. In the pharmaceutical division Roche pursues a decentralized research strategy, operating three large and independent research facilities: Roche Pharma (pRED) in Basel, Genentech (gRED) in USA and Chugai in Japan. Roche believes that “this diversity increases (its) chances of discovering new active substances. Upon achieving

¹⁹⁴ Kester et al. (2011)

¹⁹⁵ For the purpose of this thesis, I will focus only on the Pharmaceutical division.

proof of concept in the clinic, all three research units pass molecules to the Pharma division, which (selects) and develops them into medicines” (John Reed Interview, 2017, pp. 6-7) Roche's innovation network in the pharmaceuticals division thus comprises the complete ownership of Genentech since 2009, leader in biotechnologies, and majority stake in Chugai. The relationship with Chugai started out as a strategic alliance in 2002 and it is the outcome of a merge between Roche Japan and Chugai with the objective to create a leader Japanese pharmaceutical company in prescription drugs. Furthermore, the company’s research capabilities are augmented by collaboration and worldwide alliances with universities, research institutes and biotech companies, that help Roche developing individual products and expand its product portfolio (Figure 58). This network thus promotes diversity in research approach, allowing access to new technologies and promising drug candidates.

3.1.1 SWOT Analysis

Table 3 Roche SWOT Analysis

Strengths	Weaknesses
Strong R&D capabilities help Roche in keeping its product pipeline robust	Dependence on mature markets
Wide product portfolio	
Opportunities	Threats
Developments made by the group in its key pharmaceutical products	Biosimilars could be a long-term threat to Roche's mAb therapies
Launch and approvals for new diagnostic tests and molecular testing systems	Cost containment pressure in healthcare spending
Strategic acquisitions would help the group in its business growth.	Regulatory compliance problems could affect the group's operating costs.

Source: Elaborated from MarketLine, 2016

3.3 Roche Corporate Strategy

Pharmaceutical companies are facing an incredibly challenging environment: more stringent regulation, cost-pressures from payers and the concern of declining returns growth rate. Roche response to the challenges coming from the external environment is very clear: be focused on innovation, on true medical differentiation, on patients benefits, increasingly leveraging the synergies between its two core business (pharma and diagnostics) in order to thrive new tailored solutions in personalized healthcare while providing value for all its stakeholders. Roche’s key competitive advantage is, as a matter of fact, the leverage between Pharmaceutical and the Diagnostic businesses. Having the two business under one roof makes Roche uniquely positions in the industry; in particular allowing it to exchange know-hows and expertise at the very early stage of R&D, a situation in which any independent companies were to overcome many hurdles in order to enjoy the same advantage. The key strategic drivers defined by Roche for its pharma division, through which it aims at succeeding in this challenging environment, are grounded in three main pillars that define Roche’s growth strategy¹⁹⁶:

- IV. **Focus** on innovation, redefining the standard of care;
- V. **Expand** into emerging markets, improving patients’ access to medicines.
- VI. **Protect** patients with high standards by ensuring governments set adequate guidelines for the development of biosimilars.

¹⁹⁶ David Loew, Roche Investor Day (2012)

3.2.1 Innovation and R&D in Roche

As outlined above, Roche has a strong track record of innovation; since the '90s through the past two decades, it has focused on large clinical unmet needs and on transforming the field of medicine. The fact that it will launch six new medicines in a two years' time period demonstrates its commitment to innovation, in a moment when the company is facing competition to its core business. Despite recent competition, on the innovation side, Roche has always shown above-average R&D success rate. A fundamental topic for the long-term success of the industry is definitely R&D productivity and this is also at the heart of Roche since its strategy is entirely founded on innovation. In the last decade R&D returns in the pharma industry, as previously highlighted, have been declining and studies would suggest that the industry overall is going through a critical zone earning approximately on average 8-10% return, which makes it hard for companies to even earn back their cost of capital¹⁹⁷. Nevertheless, what is really important for an investor is not the industry average, but the R&D productivity across the different players. In particular, when analysing the position of Roche over ten years period on the basis of its average annual R&D spending and the outcome of its investments in the form of NMEs, a 4x difference in productivity can be observed between Roche and its peers. In other words, the best performing companies get out four times for each single US\$ that is invested in R&D compared to the least performing companies.

How does Roche manage its R&D? It possible to highlight three basic success factors¹⁹⁸:

- IV. **In-house cutting edge science:** this implies understanding the disease in order to increase the likelihood of selecting the right target and move the right opportunities through the pipeline. One possible indicator is patent application and it is clear that among its peers, Roche has a leading position. Its focus is on translating science into patient benefit and to do so Roche tries to provide a culture of empowerment and a decentralized management approach in decision-making. This is why Roche organized itself in decentralized units and kept its centres independent within the Roche Group.
- V. **R&D resource allocation:** there are always more projects and opportunities than funds. This means that there must be constant trade-offs decisions; it must be decided early enough to invest enough resources in the most promising projects and likewise kill the less promising ones. The decision-making, the governance of how to allocate resources across the different opportunities is crucial.
- VI. **Continued focus on innovation:** the right balance between internal and external innovation. Currently Roche has 150 on-going active partnerships and this is important for Roche since about a third of its total R&D pipeline compounds (phase I to III) as well as pharma sales stem from third parties relations.

3.3.1 Resource Allocation

Resource allocation process at Roche, which mainly concern investing and optimizing resource at the R&D level, and product selection is performed at the highest corporate level. In particular, there are various steps in the decision-making process concerning R&D funds allocation and molecules selection, largely guided by the Corporate Executive Committee (CEC):

- V. The first step is setting the overall risk appetite for the company. Roche selects how much it wants to spend on R&D overall and given its innovation-based strategy it is clear that it invests over-proportionally compared to the industry level. At the same time given the challenges of the business environment and the inherent risks of the market, Roche commits itself to keep its research and development's spending stable in absolute terms in the medium term.
- VI. The following step, typically on an annual basis, involves the definition of the budget for the respective units: diagnostics, research and early stage development (REDs - both pRED and gRED), late stage and the budget for Chugai, as its main partner.
- VII. An R&D steering committee, a sub-committee of Corporate Executive Committee (CEC) is then in charge of reviewing the budget allocation for the different disease areas.

¹⁹⁷ Daniel O'Day, Roche Pharma Day, 2015.

¹⁹⁸ Severin Schwan, Roche Investor Day (2012).

VIII. Lastly, three to four times a year *Lifecycle Investment Point (LIP)* transition decisions take place; during these meetings decisions are taken concerning the moving forward of specific medicines to the late stage development and the company’s commit to late stage trials.

6.3.2 Portfolio Product Optimization at the Affiliate level

In the Italian Roche affiliate, as well as in all other countries affiliate, a specific framework for portfolio prioritization (Figure 2) is being used to lead informed discussion on how to optimize local investment decisions. In particular, the key benefit of implementing such framework in local teams is to rely on a consistent and robust approach for investment decision-making, triggering and focusing the local management’s dialogue on the right questions. The outcome of this framework should also consider the downstream implications of investments decision on the change of investment mix for each product as well as the actions to undertake to execute and support new channel mix. The portfolio prioritization framework thus includes four key steps:

Figure 85 Affiliate’s Portfolio Prioritization Framework



Source: Roche Internal Data

6.4 Look at the future: Biosimilars’ Threat

As previously highlighted, the main challenges Roche will face in the coming years are biosimilars. FDA defines biosimilars as: “A biological product the is highly similar to a US licensed reference biological product notwithstanding minor differences in inactive components and for which there are no clinically meaningful differences in terms of safety, purity and potency of the product” (FDA, 2017). The introduction of biosimilars in the established as well as in emerging markets is an extremely important tool to encourage competition, especially in light of the high costs associated to the existing branded drugs, that can reduce expenses while increasing access to medicines. Indeed, biologics are among the highest-cost treatments available on the market and the price offered by biosimilars are drastically cheaper than their patented counterparts; Thus representing a lower-cost alternative, which is not only attractive but also indispensable in economies where expensive treatments are not financially feasible. Among other drivers for the introduction of biosimilars to the market, beside the potential for a lower cost alternative, there is the possibility to improve healthcare access while at the same time stimulating competition and thus contributing to the financial sustainability of the overall healthcare system. Nevertheless, despite the incredible advantages, there have several regulatory uncertainties related to the demonstration of interchangeability and automatic substitution between the originator drug and the biosimilar. Biosimilars are indeed the “hot topic” nowadays in the pharmaceutical world: their undertaking in the EU market can be viewed both as a threat or an opportunity and may drive (and has already driven) changes in many companies’ strategic responses. Obviously as of today, no one knows exactly which strategy, undertaken by the lead players, will reveal to be the winning strategy. Nevertheless, Roche position towards biosimilars so far is quite clear and its position is stated in the media release reviewed in 2016: “Roche is committed to meet high ethical standards in all its undertakings and to sustain and defend the trust of doctors who prescribe and patients who rely on the quality, safety and efficacy of our products. While Roche respects the legitimate

undertakings of its competitors, including biosimilar manufacturers, we expect that our competitors comply with applicable laws and regulations” (Media Release, 2016, p.1).

Strategic responses any pharmaceutical firm can employ can either be short term answers or on the other can take longer times to set up and have thus an extended impact on the overall corporate strategy. Among the short term responses a firm can pull out there are:

- *Differentiation* through a better safety and efficacy profile or by providing services beyond the pill to retain the patients’ pool.
- *Lobbying* for the development of a well-defined regulatory framework in line with the firm interests in order to avoid automatic substitution with the biosimilar.
- Offering a *competitive pricing* and an aggressive contracting in order to create a sort of oligopoly market.

On the other side of the coin there are all long-term strategic options:

- The need for innovation by **investing in internal R&D** and developing new products to commercialize. Indeed, for pharmaceutical companies R&D is the main “asset” to create and maintain competitive advantage in the future. Indeed this has been and still is Roche strategy, holding in pipeline numerous NMEs with 20 years of patent protection ahead and 12 new potential blockbusters (e.g Ocrelizumab in multiple sclerosis).
- Developing **commercial strategies aimed at extending a product lifecycle**, for example by improving the dosage regimens, investing in a reformulated version or finding complements to existing products. For example the switch to a simplified dosage from IV to SC as it has been the case for Roche’s Rituximab or Herceptin can lead to sales increase and a delay in competition. Even though the introduction of a redesigned product, an improved version of the originator drug, has its investments in clinical trials, it has lower R&D costs and higher eligibility for patent protection. Develop products along the same therapeutic algorithm that can function, as complement to an existing marketed product can be helpful in postponing competition.
- A further strategic option is the possibility to **internalize external R&D through M&A or strategic alliances**. M&A, as a matter of fact, must not be performed to be the only large company in the market, but rather to maintain leadership position. Acquisitions should go “deep, not broad” aimed at fueling the core business and areas of strength, by acquiring smaller biotech companies with promising drug concepts in early stages. At the same time, strategic alliances and partnerships are ways to “internalize” external innovation and leverage on the combine knowledge and know-hows. Roche definitely prefers internal growth strategies, without relying too much on M&A activities. Nevertheless, it preserves an active network of partnerships spanning over 150 alliances. One of the most recent example of strategic R&D collaboration for Roche is the one it entered in 2015 with Foundation Medicine (FMI), acquiring a majority stake of 53.6%

Roche’s innovation-based strategy and its focus on areas of highly unmet need, has driven and it will continue to fuel its growth. In light of its corporate strategy, its portfolio strategy emphasises both the attention on growing and optimizing the existing business by improving the current standard of care as well as expanding the business through advanced diagnostics and differentiated medicines, by concentrating in new therapeutic disease areas, outside oncology – its comfort zone.

Conclusion

In conclusion, it is fundamental for pharmaceutical companies to strengthen PM decision-process, reallocating capital across businesses away from underperforming R&D assets and mature markets that can no longer sustain big sales forces, while investing in those that will represent future cash cows. What remains still unknown is whether corporate management will test their level of readiness, be agile enough, to accommodate the industry’s fundamental changes. To what extent corporate strategies will accommodate current market opportunities and challenges? How would Big Pharma reconfigure their R&D pipeline to adjust their current portfolios of business units and marketed products to adapt to the change? Winning pharma companies all have to make tough choices about where—and where not—to focus their efforts and investments. While some choices may not immediately popular with the markets and stakeholders, companies needs to make informed portfolio decisions on their competitive R&D strategy in order to emerge as winners in the industry.