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R&D and Product Engineering in Global Pharmaceutical Companies

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Abstract

Innovation and imitation processes play a major role in business development strategies of global pharmaceutical companies. In this study, we have analyzed some of the largest originator and generic pharmaceutical companies worldwide to determine which key features characterize such companies with a particular emphasis on new drug R&D processes.

Keywords: Global Market; Pharmaceutical Company; Innovation; R&D; Drug Discovery; Product Engineering

1. The Global Pharmaceutical Market

The pharmaceutical market is one of the most R&D-intensive industries, with innovation being the main driver of its dynamics.

Historically, this market has been dominated by global pharmaceutical companies also known as originator, branded, or patent-based firms. Over the years, these corporations have heavily invested in R&D and innovation to limit competition and consolidate their competitive advantage.

In addition to global pharmaceutical companies, other bodies, such as generic pharmaceutical firms, small and medium specialized companies, nation-states and national or supranational organizations [e.g. World Health Organization (WHO), European Medicines Agency (EMA), Food and Drug Administration (FDA), Therapeutics Goods Administration (TGA), Adverse Drug Reactions Advisory Committee (ADRAC), Agenzia Italiana Farmaco (AIFA), etc.], have played a crucial role in setting norms and standards that regulate the pharmaceutical market worldwide.

In this regard, it is well established that nation-states operate on their domestic pharmaceutical market as both payers and regulators with the aim of protecting human health and community well-being. In doing so, they can authorize new product sales and influence the supply and demand through regulation of patents, distribution channels, and advertising. They can also sponsor R&D programs leading to new drug discovery.

Furthermore, in order to control public pharmaceutical expenditures, each individual State may intervene in price regulation, pharmacological agent

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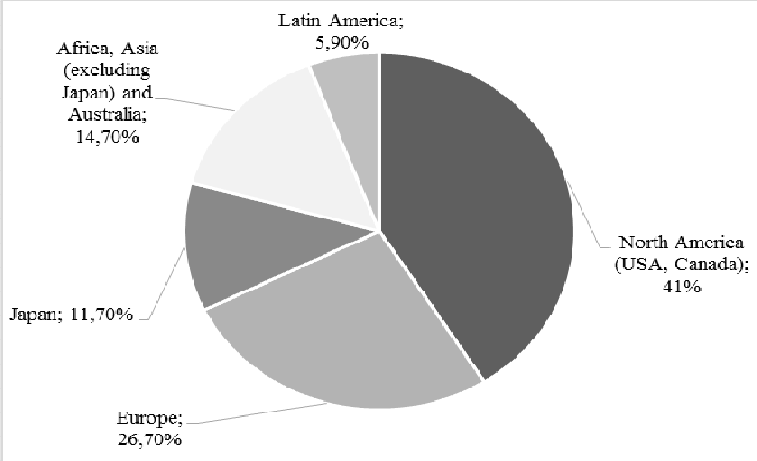
classification, and reimbursement criteria; all measures that can directly influence the demand and sales value of drug products.

In recent years, drug demand has been steadily increasing. In 2012, pharmaceutical sales reached a total of $ 857,800 million at ex-factory prices (Efpia 2013). A large part of these sales came from the US and Canada followed by Europe - particularly France, Germany, Italy, Spain, and the UK - and Japan.

Likewise, over the years, a significant increase in pharmaceutical sales has also been observed in pharma-emerging markets such as China, India, Brazil, and Russia (IMS-Institute for Healthcare Informatics 2013) probably due to demographic, economic and epidemiological changes that have taken place in these new economies. Such positive trend can also be attributed to broader changes in corporate development policies as well as improved state and private insurance funding for primary healthcare and medications. On the other hand, the drug sales downturn observed in developed markets is thought to be due to the financial and economic crisis, which has led to austerity measures in the healthcare system. This negative trend was further exacerbated by the increasing availability of lower-cost generic versions of brand-name drugs after their originator's patent expired.

Figure 1: Pharmaceutical Sales by Area



Source: Adapted from Efpia and IMS MIDAS 2013 (Data Relate to the 2012 Audited Global Retail Pharmaceutical Market at Ex-Factory Prices).

It is well established that customers willing to spend their money on healthcare are those sustaining the demand for pharmaceutical products. Thus, the demand for a pharmaceutical product, hereinafter referred to as derived need (e.g. drug), occurs as a result of the demand for a generic need (e.g. health). Since customers don't have the necessary medical knowledge to fully evaluate the benefits of a certain drug treatment, they seek advice on this matter from their doctors (Riboldazzi 2012), who, consequently, become major determinants of the demand for pharmaceutical products, especially with regard to ethical drugs.

Furthermore, the low price elasticity of pharmaceutical products with respect to their demand is the direct result of a supply system that can only offer products hardly replaceable by drugs used in other therapeutic areas. This lack of viable

substitute drugs is also due to the long period of patent protection granted to the originators, which, practically, makes it impossible to replace pharmacological products with other equivalent generics.

Generally, the supply system appears to be heterogeneous in nature and mostly concentrated in the hands of a few large pharmaceutical companies, defined as originator or branded firms, flanked by large generic pharmaceutical companies as well as smaller companies in terms of both product out-put and market share. These latter ones are small/medium firms specialized in producing drugs according to specific indications or pharmaceutical formulations or, alternatively, focused on innovation with regard to a well-defined and restricted sector.

Competition, therefore, arises from competitive action-reaction mechanisms carried out by leader-follower companies based on innovation and imitation processes developed and carried out on a global scale.

2. Pharmaceutical Companies in the Global Market

Table 1 shows the main global pharmaceutical companies in terms of prescription drug sales.

Table 1: *Worldwide Prescription Drug Sales in 2012. Top 20 Companies*

Company	*Country*	*Revenues ($ bn) Year 2012*	*Revenues ($ bn) - Year 2018 (forecast)*
Novartis	Switzerland	45.4	52.3
Sanofi	France	38.4	49.0
Pfizer	United States	47.4	46.8
Roche	Switzerland	37.5	46.3
GlaxoSmithKline	United Kingdom	33.1	40.1
Merck & Co	United States	41.1	40.0
Johnson & Johnson	United States	23.5	26.0
Novo Nordisk	Denmark	13.5	21.7
Bristol-Myers Squibb	United States	13.2	21.7
AbbVie	United States	23.1	21.3
Gilead Sciences	United States	9.4	21.3
AstraZeneca	United Kingdom	27.1	21.0
Bayer	Germany	14.7	19.4
Takeda	Japan	15.2	17.7
Amgen	United States	16.6	16.4
Teva Pharmaceutical	Israel	17.7	15.8
Eli Lilly	United States	19.7	15.4
Boehringer Ingelheim	Germany	14.7	12.7
Baxter International	United States	8.9	12.1
Astellas Pharma	Japan	11.0	12.1

Source: Adapted from EvaluatePharma, *World Preview 2013. Outlook to 2018. Returning to Growth*, June 2013.

The majority of these companies, which are known as originator or branded pharmaceutical companies as opposed to those that operate in the generic drug

market, is mainly focused on innovation and R&D and characterized by the frequent use of patents availing temporary and advantageous monopoly positions.

In particular, the innovation pursued by branded pharmaceutical companies can be classified as follows (EGA 2007):

- breakthrough innovation: consisting of a new genuine approach to a disease or a New Chemical Entity (NCE);
- stepwise innovation: referred to as new molecules of one chemical family offering differences in properties such as indications, side effects, and drug metabolism;
- incremental innovation: consisting of new dosage forms and new formulations.

In relation to the terms of innovative drug patent protection, generic companies become part of the global pharmaceutical market (Table 2). They compete against branded pharmaceutical companies focusing on production process efficiency in order to produce copies of the originator's products offered at lower prices thanks to lower incurred R&D costs.

Table 2: *Worldwide Generic Drug Sales in 2012. Top 20 Companies*

Company	*Country*	*Revenues ($ bn) - Year 2012*
Teva Pharmaceutical	Israel	9.6
Novartis	Switzerland	7.8
Actavis (Watson Pharmaceuticals)	Ireland	6.3
Mylan	United States	5.6
Sanofi	France	2.4
Hospira	United States	2.2
Daiichi Sankyo	Japan	2.2
Sun Pharmaceutical	India	1.9
Aspen Pharmacare	South Africa	1.9
Dr. Reddy's Laboratories	India	1.6
Lupin	India	1.6
STADA Arzneimittel	Germany	1.6
Cipla	India	1.4
Apotex	United States	1.4
Fresenius	Germany	1.4
Krka Group	Slovenia	1.2
NichiIko Pharmaceutical	Japan	1.1
Valeant Pharmaceuticals	United States	1.1
Sawai Pharmaceutical	Japan	1.0
Par Pharmaceutical	United States	1.0

Source: Adapted from EvaluatePharma, *World Preview 2013. Outlook to 2018. Returning to Growth*, June 2013.

A generic drug is a pharmaceutical product, usually intended to be interchangeable with the innovator product, which is manufactured without the need of a license provided by the innovator company and marketed after the expiry date of the patent or other exclusive rights (WHO). Basically, a generic medicine contains the same active substance as the reference medicine and is used with the

same dosage to treat the same disease as its equivalent branded drug (European Generic Medicines Association).

In the global pharmaceutical market there are different types of generic medicines:

- *Generic unbranded medicines*. These products are sold under the generic scientific name of the active ingredient corresponding to the International Nonproprietary Name (INN). Information about the marketing authorization holder is disclosed as well;
- *Generic semi-branded medicines*. These drugs are marketed under the INN followed by the name of the producer;
- *Generic branded medicines or copies of innovative drugs bearing a trade mark.* These drugs may be the result of business diversification strategies implemented by the originator company to increase total sales volume while limiting market entry of pure generic drugs. All these measures are put in place by the originators in order to prevent their competitors from gaining market share.

The analysis of some of the largest originator and generic pharmaceutical companies reveals several common characteristics:

- *Global sales and localization choices unconstrained by geographical boundaries.* To take advantage of temporary and contingent market opportunities, pharmaceutical business development is often based on decisions relying on procurement, production, and distribution policies transcending local boundaries. Careful analysis of six among the main originator and generic companies by revenue shows a uniform geographical distribution of their operations to best support their business strategies (Figure 2).

Figure 2: Sales by Area and Geographical Distribution of Six Among the Main Originator and Generic Companies

Novartis	***Sanofi***	***Pfizer***
Novartis sells its products (e.g. pharmaceuticals, eye care, generics, vaccines, over-the-counter and animal health medicines) in more than 150 countries totaling 36% of sales in Europe, 33% in the United States, 22% in Asia, Africa, and Australia and 9% in Canada and Latin America. Novartis has R&D centers located in America, Europe, and Asia: 8 Novartis institutes for biomedical research, 7 pharmaceutical development sites and 2 vaccine sites.	Sanofi sells its products in over 100 countries totaling 33.3% of net sales in Emerging Markets, 31.7% in the US, 23.8% in Western Europe and 11.3% in the rest of the world. Sanofi has 112 industrial sites in 41 countries - 82 pharmaceutics sites, 12 vaccine sites, and 18 animal health sites - and more than 20 R&D sites. The company has also more than 110,000 collaborators worldwide - 53,880 in Europe, 18,795 in North America, 39,453 in other countries.	Its revenues, in 2013, exceeded $500 million in 12 countries outside the US. The US represents its largest market contributing to 39% of total revenues (2013). Japan is responsible for more than 10% of total revenues (2013). Pfizer has R&D colleagues across the world to support its pipeline. Major Research and Development locations are as follows: Andover (MA), Cambridge (UK), Cambridge (MA), Groton (CT), La Jolla (CA), Pearl River (NY), San Francisco (CA), Sandwich (UK), St. Louis (MO).
Teva	***Sandoz (Novartis)***	***Actavis* (*Watson Pharmaceuticals)***
Teva operates in 60 countries and distributes products all over the world. Teva revenues are distributed as follows: 52% in the USA, 29% in Europe (all members of the European Union, Switzerland, Norway, Albania and the countries of former Yugoslavia) and 19% in the rest of the world (primarily in Japan, Canada, Latin America, Israel and Russia). Teva has 50 pharmaceutical plants in North America, Europe, Latin America, Asia and Israel, with two additional sites currently under construction. Teva's generic division accounts for 49% of total group sales (42% in the US, 35% Europe, 23% rest of the world).	Sandoz sales are distributed as follows: 50% in Europe, 31% in the United States, 12% in Asia, Africa, and Australasia, 7% in Canada and Latin America. Sandoz sells its products in over 160 countries, employs more than 26,500 people and has six global development centers and a worldwide network of 45 production sites located in Canada, USA, Mexico, Brazil, Poland, Germany, Austria, Italy, Spain, Slovenia, Romania, Algeria, Turkey, India, Bangladesh, Indonesia, China, Japan and South Africa.	Actavis has 20 R&D sites - 6 in America, 9 in Europe, and 5 in Asia - and more than 30 manufacturing facilities. Actavis Pharma, which includes the generic, branded generic, legacy brand and Over-the-Counter (OTC) division, accounts for approximately 75% of the company's total net revenues (year ended 2012) and makes 62% of its sales in the US and 38% in the rest of the world.

Source: Adapted from Actavis Annual Report 2012, Novartis Annual Report 2013, Sandoz Facts&Figures 2013, Teva Annual Report on Form 20-F 2013, Pfizer Financial Report 2013, Sanofi Annual Results 2013, www.novartis.com, en.sanofi.com, www.pfizer.com, www.teva.com, www.sandoz.com, www.actavis.com.

- *Large size and global development.* Mergers and acquisitions (M&A) have always played an important role in the growth of both originator and generic

pharmaceutical companies. Novartis, for instance, was created through the merger of Ciba-Geigy and Sandoz and, over the years, has acquired many other companies including Lek Pharmaceuticals, which was originally a Slovenian generic pharmaceuticals company acquired by Sandoz, the worldwide adult medical nutrition business of Mead Johnson and Company, a subsidiary of Bristol-Myers Squibb, and a majority interest in Idenix Pharmaceuticals (US). Furthermore, the company has acquired the Danish firm Durasacan A/S; Sabex Holdings Ltd. (Canada); Hexal AG, a leading generics company based in Germany; and Eon Labs, an American generics company. Finally, Novartis acquired the North American OTC brand portfolio of Bristol-Myers Squibb, Chiron Corporation, Alcon Inc., and Fougera Pharmaceuticals Inc. (acquired by Sandoz).

The goal behind M&A strategies is to generate synergism and gain access to new markets and therapeutic areas, which ultimately can lead to enhanced growth and global development. Further objectives of M&A activities include the exploitation of economies of scale and scope in research and development, as well as production and distribution of pharmaceutical products.

In this regard, several important M&A activities involving pharmaceutical companies are finalized each year. In 2012, for example, the following transactions, involving both large and small/medium companies – with the first company mentioned being the buyer, and the second one the target company – were sealed: Gilead Sciences and Pharmasset; Bristol-Myers Squibb, AstraZeneca and Amylin; Watson Pharmaceuticals and Actavis; GlaxoSmithKline and Human Genome Sciences; Valeant Pharmaceuticals and Medicis Pharma; Bristol-Myers Squibb and Inhibitex; Novartis and Fougera Pharma; AstraZeneca and Ardea Biosciences.

- *Product portfolio management of different business segments.* Large pharmaceutical companies manage a complex product portfolio related to different business segments that enables them to gain control of diverse marketing areas while preserving growth and profitability.

In this scenario, it has become common practice for originator and generic companies seeking to expand their product pipeline to open and develop both generic and originator drug divisions within their corporate structure. This way, they manage to develop novel specialty products in different key therapeutics areas.

Furthermore, pharmaceutical companies are heavily involved in the production of over-the-counter (OTC), biological, and biosimilar products.

OTC products, generally available in small packages, refer to drugs containing active ingredients already widely used in medicine for short-term therapies to relieve symptoms of illnesses that can be easily diagnosed by the persons suffering from them.

On the other hand, biological products contain an active ingredient which is usually produced or extracted from a biological system or derived from a biological source through biotechnology methods. Thus, they are often referred to as biotechnological drugs.

Biosimilar products are similar to originator biologicals but are no longer subject to patent protection. Therefore, they can be produced by pharmaceutical companies in accordance with standards set out by specific guidelines at a lower price than that of branded biological products.

In addition to the products mentioned above, pharmaceutical companies can develop and sell animal health products, diagnostic products, and vaccines with regard to different therapeutic areas.

- *Large Corporate R&D investment*s. A large part of the revenues originated by pharmaceutical firms – specifically with reference to originator companies – is invested in R&D activities, which are characterized by high costs and uncertain outcome (Table 3).

Table 3: *Pharmaceutical R&D Expenditure. Year 2012. Top 20 Companies*

Company	*Country*	*Pharma R&D Spending ($bn)*
Novartis	Switzerland	8.8
Roche	Switzerland	8.0
Merck & Co	United States	7.9
Pfizer	United States	7.0
Sanofi	France	6.1
Johnson & Johnson	United States	5.4
GlaxoSmithKline	United Kingdom	5.3
Eli Lilly	United States	5.1
AstraZeneca	United Kingdom	4.5
Takeda	Japan	3.9
Bristol-Myers Squibb	United States	3.7
Boehringer Ingelheim	Germany	3.3
Amgen	United States	3.3
AbbVie	United States	2.8
Bayer	Germany	2.5
Astellas Pharma	Japan	2.2
Novo Nordisk	Denmark	1.9
Gilead Sciences	United States	1.7
Celgene	United States	1.4
Biogen Idec	United States	1.3

Source: Adapted From EvaluatePharma, *World Preview 2013. Outlook to 2018. Returning to Growth,* June 2013.

In this regard, it is estimated that the cost associated with R&D activities of a new chemical or biological entity is approximately $ 1,506 million and only one or two out of 10,000 compounds synthesized in the laboratory will be able to successfully go through all the development stages required to become a marketable medicine (Efpia 2013).

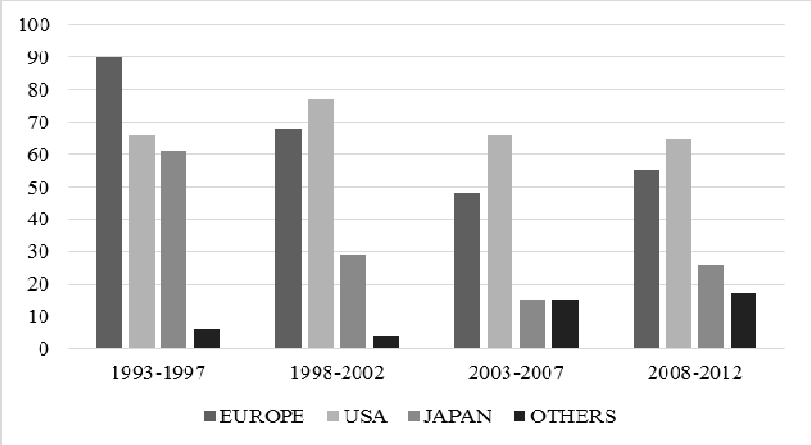
In 2012 about 30,000 million euros in R&D were invested by pharmaceutical companies in Europe (Table 4) and, although the largest investments in R&D were made in the US (Figure 3), there was also a significant increase of investments made in emerging markets, in particular China, Brazil, and India.

Table 4: *Pharmaceutical R&D Expenditure in Europe, US, and Japan (Millions of National Currency Units). 1990-2012.*

	1990	1995	2000	2005	2011	2012
EUROPE (€ million)	7,766	11,484	17,849	21,988	29,192	30,000
USA ($ million)	6,803	11,874	21,364	30,969	36,374	36,810
JAPAN (¥ million x 100)	5,161	6,422	7,462	10,477	12,299	n.a.

Source: PhRMA, JPMA, EFPIA Member Associations, EFPIA Key Data 2013.

Figure 3: Number of New Chemical or Biological Entities by Area (1993-2012)



Source: SCRIP – EFPIA Calculations (According to Nationality of Mother Company), EFPIA Key Data 2013.

- *Shareholder value creation.* Large pharmaceutical companies are well aware of the central role played by local and global stakeholders in good corporate governance. In this regard, corporate strategies call for rigorous financial analysis of returns on capital and are often influenced by the main goal of promoting value for shareholders.

- *Activation of competitive strategic alliances.* Different types of alliances are forged by large pharmaceutical companies specifically with regard to the production and distribution of medicinal products and the various stages of new drug discovery. Thus, alliances, such as R&D partnerships, outsourcing, co-production, co-marketing, and licensing, are undertaken together with other large pharmaceutical companies, biotech companies, small/medium pharmaceutical companies, universities, and research centers or other subjects specialized in particular activities or operating in certain areas in order to develop innovation, improve R&D productivity, and, more generally, contain process costs while taking

advantage of the knowledge and skills of different partners in a collaborative network approach.

3. R&D and Product Engineering in Pharmaceutical Companies

Innovation in pharmaceutical companies has been extensively examined with regard to specific research areas (Alexander et al. 1995; Chiesa 1996; Jungmittag et al. 2000; DiMasi et al. 2003; Hara 2006; Gassmann et al. 2008; Magazzini et al. 2009).

In this regard, innovative strategies play a crucial role in the growth policies of pharmaceutical companies. The development of a new product is the result of a complex set of activities that create articulated links between employees, external structures, and co-makers, shaping a competitive network able to manage R&D, production, marketing, and finance in a global business perspective (Brondoni 2009).

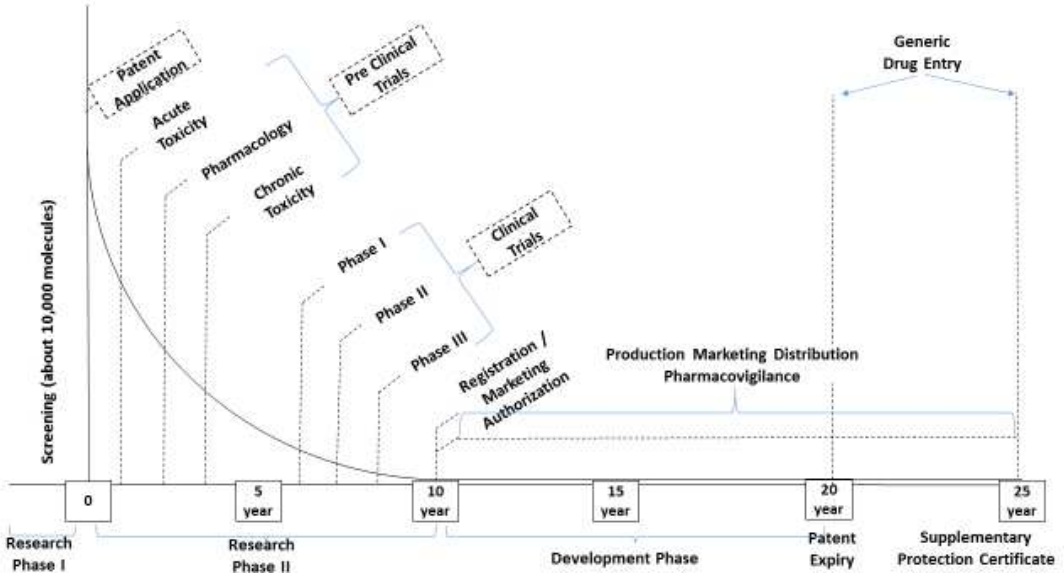
Basically, in a pharmaceutical company, the innovation development process starts with the basic research, which generates basic knowledge and skills required to develop the R&D and design/engineering process of the new product. This process includes: preliminary design, product engineering, process engineering, industrial production, and new product launch on the market.

3.1 New Drug R&D Process

Originator drug discovery is a lengthy and complex process characterized by high costs and uncertain outcome (Figure 4). The research starts with the identification of a 'target', usually a protein or a gene, involved in a particular disease. After target validation, companies look for a molecule, called lead compound, which, by acting on the target, can affect disease progression. To this end, thousands of molecules are screened to determine their efficacy as agonists or antagonists of a given target molecule. The initial screening is usually performed by means of High Throughput Screening (HTS) methods, which allow random screening of a large number of compounds leading to the selection of those with a therapeutic potential.

Only about 1% of these molecules will be considered a pool of potential lead compounds. These latter ones will then be optimized or altered through chemical or genetic engineering methodologies to make them more effective and safer.

Figure 4: Phases of the New Drug R&D Process



Source: Adapted from www.fda.gov; www.ema.europa.eu; www.agenziafarmaco.gov.it; Efpia, *The Pharmaceutical Industry in Figures*, 2013; PhRMA, *Drug Discovery and Development. Understanding the R&D Process*, 2007.

This first phase is defined as *basic research phase* (*research phase I*) and is followed by the *applied research phase* (*research phase II*), which is a relatively long experimentation process to evaluate efficacy and safety of the compound.

During these two research phases, originator pharmaceutical companies expose themselves to high-risk investments with no economic returns on investment. In order to minimize this financial risk and ensure future profitability, companies tend to apply for patent protection starting from the discovery of the active substance, even if, by doing so, they shorten the overall duration of the patent.

In particular, the *applied research phase* (*research phase II*) includes *preclinical* and *clinical trials*.

Preclinical trials (i.e. *in vitro* and *in vivo* tests) evaluate the molecule behavior along with its level of toxicity and chemical-physical characteristics in order to determine any composition changes in view of the quantities expected to be used in clinical trials.

The clinical phase is initiated only after the preclinical phase has come to an end; this phase, which evaluates the candidate drug safety and effectiveness in humans, consists of three different stages.

The first stage aims at providing an initial assessment of the safety and tolerability of the drug; in particular, a limited number of healthy volunteers are selected to take a certain dosage of the drug being tested. The main objective is to determine the tolerability and side effects of the drug. If the drug has an acceptable level of toxicity compared to the expected benefit, the so-called benefit/risk profile, the next trial phase begins. In the first stage of clinical trials, during which about 70% of the molecules are eliminated, the pharmaceutical companies may further perfect the product to determine the safe dosage range.

In the second stage, the level of molecule skimming is much lower, and the goal is to evaluate the therapeutic effectiveness as well as short-term side effects and risks, while, at the same time, trying to find the optimal dosage strength and schedule for drug administration. In this regard, tests are carried out only on volunteer patients suffering from a certain disease.

The clinical phase continues with a third stage involving a larger number of patients – hundreds, thousands of them located in different centers – and is designed to confirm the efficacy, refine dosage, evaluate side effects, and the individual safety and variability. This phase can also provide the basis for labelling instructions to help ensure proper use of the drug.

Once this testing phase is over, pharmaceutical companies can submit an application for the new drug registration to the appropriate regulatory agencies in different countries [e.g. Food and Drug Administration (FDA) in the United States; Agenzia Italiana Farmaco (AIFA) in Italy etc.].

In the eurozone, pharmaceutical companies can apply to the European Medicines Agency (EMA), which oversees a centralized registration process that allows the companies themselves to sell the product throughout Europe.

Alternatively, firms may request a decentralized authorization; in this case, after obtaining permission from the competent national agency, a mutual recognition by other countries is usually required.

At this point the *product development phase* begins and pharmaceutical companies start the industrial production of the new drug. Thus, the preliminary design and the product engineering phase - which defines product architecture, choice of components, and physical and conceptual links between such components - are followed by the process engineering phase - which includes a designing production phase, manufacturing cycle, and other tasks that must be completed to develop the product - and finally by the product industrial realization and launch.

Subsequently, drug manufacturing involves scale-up procedures that allow companies to switch production from milligrams to grams, kilograms or tons in order to optimize all the parameters involved in the synthesis of the active ingredient while maintaining a good reproducibility of the process and controlling how reaction conditions vary with the increase in the quantities produced.

In this regard, the drug manufacturing process should ensure compliance with the strict regulations of good manufacturing practices (GMP), which, regardless of differences among countries, establish rigorous quality standards in accordance with current legislation. To obtain GMP certification, companies must prove that plants and equipment are in good working conditions and comply with approved procedures for procurement, production, packaging, logistics, and storage operations.

The process of new drug R&D is generally managed by the pharmaceutical companies according to the sequential engineering method based on a rigid division of jobs and operation processes organized sequentially so that each step is worked on in a certain order, especially in the basic and applied research phases.

Nevertheless, in order to achieve cost reduction, efficiency, and flexibility, companies organize certain processes in a parallel way to reduce time-to-market. This measure stretches the period of exclusive sales granted by the patent coverage with consequent advantages for those who work as monopolists.

Indeed, globalization has led to dramatic changes in the process of R&D and product engineering of innovative drugs, which is now characterized by a fragmentation of the various phases that are often outsourced overseas to take advantage of opportunities offered by the global market. In this regard, although most of the overseas R&D by US-based pharmaceutical companies has been directed toward Western Europe, Japan, and Canada, a growing part of their R&D activities have considerably expanded in the emerging markets, especially those of China and India (PwC 2010). An increased globalization of R&D has also been observed in European and Japanese companies (Gassmann et al. 2008).

In addition to that, the creation of a collaborative network among pharmaceutical companies can favor R&D alliances, which can be formalized in agreements on outsourcing of clinical trials, co-invention (Nobuo 2011), and licensing. These open network alliances can significantly reduce R&D expenditures and lead to process optimization while giving companies access to resources that otherwise would not have been available.

The patent protection granted to originator companies prevents anyone from using and selling the novel drug. Therefore, the time between the product launch on the market and the loss of patent protection enables firms to achieve important results by consolidating or gaining market positions thanks to the absence of equivalent substitutes.

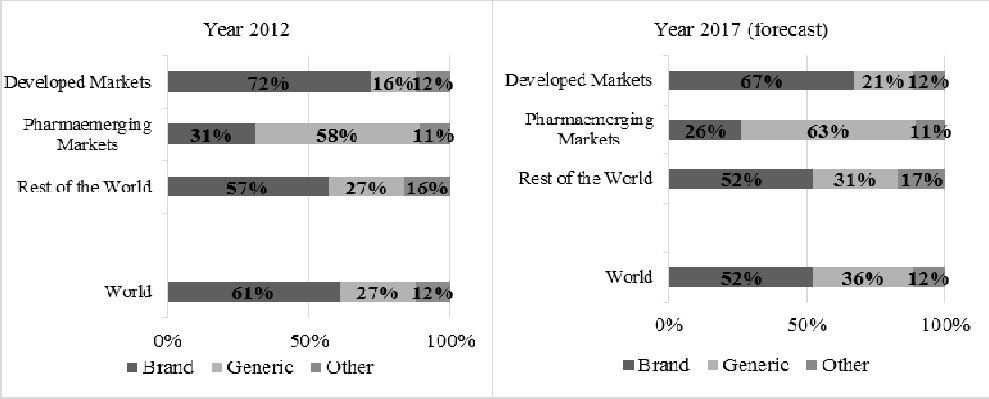
As a result, sales of a pharmaceutical product increase dramatically in the period immediately following the product launch, but then remain stable until the patent expires.

The patent expiration marks the beginning of price competition by low-cost generics that can often take away large market shares from the originator company.

3.2 Generic Drug R&D Process

The diffusion of generics depends on the degree of patent protection afforded to the originator companies (Figure 5). In OECD countries, according to the Trade Related Aspects of Intellectual Property Right Agreement (TRIPS), patent protection lasts 20 years starting from the filing date of the patent application. In fact, since the period of time between obtaining a patent and being granted marketing authorization may be quite long, the effective patent protection lasts less than 20 years. Thus, some countries, including the US and EU, have introduced special legislation to extend patent coverage after its expiration – in the EU, the Supplementary Protection Certificate extends patent protection up to 5 years; in the US, the Waxman-Hatch extends patent protection by five years with a coverage limit of 14 years from the time in which marketing authorization was granted.

Figure 5: Generic and Branded Drug Shares by Area. Year 2012-2017



Source: IMS Institute for Healthcare Informatics, *The Global Use of Medicines, Outlook Trough 2017*, 2013.

The diffusion of generics drug is often linked to other economic and/or legal factors involving pricing and reimbursement levels implemented by each country, the presence of simplified procedures for the demonstration of bioequivalence, or the opportunity to carry out research and tests for drug approval before patent expiry without having to launch it on the market before that date (i.e. Roche-Bolar provisions).

The originator company that has obtained the patent for a novel drug has the obligation to make the invention public by publishing all the relevant studies. Consequently, the new generic drug R&D and product engineering process starts from the careful analysis of all the relevant published literature. This way, generic firms are able to determine which parameters characterize the medicinal product they intend to copy [e.g. quantitative composition, characterization of the active pharmaceutical ingredient (API) solid state, the production process, etc.].

The new generic drug R&D and product engineering process is, therefore, based on a reverse engineering approach, which involves reproducing a real object in its functions and dimensions through the physical analysis of its components required for designing and processing.

As we mentioned above, the originator research phase is divided into basic and applied research, with the latter being carried out by means of preclinical and clinical tests. In contrast, the generic research phase starts with the study of the originator drug in order to identify its architecture and then, through product engineering, synthesize the bioequivalent copy drug with the same active ingredient, pharmaceutical form, and administration route and dosage unit as the innovative drug.

At this stage, generic pharmaceutical companies must demonstrate the chemical-pharmaceutical equivalence and the bioequivalence of the generic drug to the originator drug before being able to obtain a marketing authorization from regulatory agencies, such as EMA, FDA, and TGA. This equivalence is proved when the generic product contains the same active ingredient in the same quantity and dosage form as the originator drug. Once this equivalence is demonstrated,

generic companies are exempted from carrying out those preclinical and clinical trials that must be conducted by originator companies for novel drugs.

Bioequivalence tests the therapeutic equivalence between the potential generic drug and the reference medicinal product and consists of a pharmacokinetic study conducted on the basis of rigorous and precise guidelines – for instance in Europe two products are equivalent if the pharmacokinetic parameters confidence limits are between 0.80 and 1.25 according to the European Note for Guidance on the Investigation of Bioavailability and Bioequivalence. The bioequivalence study is based on clinical tests and is conducted on healthy volunteers to determine the bioavailability of both the generic and originator preparations.

After the demonstration of bioequivalence is completed, the *research phase* gives way to the *product development phase* where generic companies, through process engineering, start large-scale production and subsequently sell the generic product on the market usually at lower prices than those of the originator companies.

The development of generics is, therefore, a threat to branded pharmaceutical companies. In this regard, generic companies, behaving as imitators, relate to competitors for their resources organization, processes, and policies according to an outside-in approach that allows them to reduce time and costs of activities and processes, thereby achieving a competitive advantage.

Moreover, generic companies develop collaborative relationships to exploit research, production, and distribution activities of drugs. This collaborative network allows them to be effective and efficient and facilitates their access to markets for business development at a global level.

4. Final Remarks

Based on this scenario, it is apparent that the development of pharmaceutical generic companies clashes with the dominance of originator companies, which are primarily focused on innovation and the preservation of their patent rights.

In order to partially reverse this trend and maintain a leading position on the market, originator companies can choose to enter the market of generic products, producing equivalent drug and forging agreements with other companies to develop the production of generic medicines. They can also implement alternative measures such as patent thickets, multiple divisional patent applications, and follow-on patents (EGA 2008) to safeguard innovation and prevent imitation of their products.

In particular, patent thickets refer to the development of an extensive thicket or cloud of patents around a drug; the various parts of that cloud may relate to the active pharmaceutical substance, a polymorph or hydrated form of the active substance, an isomeric form of the drug, and so on.

Another common way of maintaining the uncertainty generated by patent applications is to keep a series of pending divisional applications on file. Even if a generic pharmaceutical company is successful in defeating a parent application before a patent office or a national court, the generic company is still at risk that a patent covering substantially the same subject matter may issue from a pending divisional application in the same family which may be asserted against them (EGA 2008).

Finally, follow-on medicines consist of second-generation drugs that allow branded pharmaceutical companies to file secondary patents that will ensure market exclusivity for an extended time period.

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