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A Critical Look at Innovation Profile and Its Relationship with Pharmaceutical Industry

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Abstract: ***Background: The pharmaceutical sector undertakes extensive research and development (R&D). Pharmaceutical industries have continued to launch an appreciable number of new medicines, different pharmaceutical formulations, new indications and other innovations that contribute to the growth of this sector. New novel medicines are increasingly essential for continued success given the number of standard medicines now available as low cost generics or biosimilars. Consequently, innovation is a fundamental element in pharmaceutical company competition. Not all innovations though are the same size, type or category with differentiation of innovation essential for commercial success. However, given the wide range of definitions used in the literature, the framing may diffuse. Currently, there are several types and categories of innovation are deficiently harmonized and poorly stratified resulting in analysis trends and provide major obstacles to innovation's differentiation and in assessing the company's innovative dominant characteristic in the sector. The objective of this study is to stratify and organize, didactically, the field of definitions and concepts of innovation and provide a structural and operational delineation, from a critical point of view, for the classifications of innovation applied to the pharmaceutical industry.***

Keywords: Innovation, Pharmaceutical science, Pharmaceutical novelties, Pharmaceutical technology.

1. Introduction and theorical framework

The pharmaceutical sector is the sector that invests most in Research and Development (R&D) and one of the most innovators in the market [1] when compared to other segments. Many diseases now have effective treatments to reduce morbidity and mortality as well as increase the quality of life and life expectancy [2]-[3]. In particular, the 1990s yielded several successful medicines which empowered the pharmaceutical sector and its shareholders [2].

According to Craig and Malek [4], the pharmaceutical industry has an important role to play in society. This importance stems from the joint responsibility with the medical profession for the maintenance of health, which, in itself, is already a valuable asset, as well as enhancing productivity. This is expected to continue with the discovery and development of new medicines to treat areas of unmet need [5]-[6]. In addition, innovations are essential for the continued success of pharmaceutical companies with the increasing availability of standard medicines as low cost generics and biosimilars [7] although this can be hard to achieve [8]-[9].

According to Achilladelis and Antonakis [10], innovation is a dynamic process building on the comments of Pavitt [11] that "industrial firms cannot and do not identify and evaluate all innovation possibilities indifferently, but are constrained in their search in their search by their existing knowledge and skills to closely related zones". That is the tendency that a particular industry specializes in a particular type of innovation, having more prominent characteristics for a particular category when compared to others.

Inventions or Technological discoveries applied and marketed can be grouped into different categories. However, due to the myriad of definitions for the types of innovation, there is ambiguity in perception and demarcation of these categories [12]. Defining the concept and categorizing the types of innovation is important to establish ways of operationalizing the terminology and their application in different segments [12]. This allows the establishment of standards that can sustain scientific, technological, economic

and industrial comparisons. It is only possible to expand knowledge about a potential innovation framework as the conceptual application is consolidated, giving rise to a common starting point for classifications.

The objective of this study is to stratify and organize the different fields and concepts of innovation, as well as to provide a structural and operational delineation, for the different innovations from pharmaceutical companies. Concomitantly, by elaborating a guidance structure for the different classifications, we intend to demonstrate how innovation relates to pharmaceutical companies and how the typological profile described in the literature can be framed to examples of new innovations. This builds on the concept from the OECD [13] that the minimum requirement for an innovation is that the product, process, marketing or organizational method should be new, or significantly improved for the company. Consequently, the perspective adopted to evaluate the innovative act, and assign a categorization in this paper, is an entrepreneurial one, specifically from the point of view of pharmaceutical companies. This is particularly important at this time as there are concerns with the funding of new medicines in a number of countries due to ongoing pressures from ageing populations, stricter treatment targets and the continued launch of new premium priced medicines especially in areas of cancer and orphan diseases [8]-[14]-[15]-[16]-[17]-[18]. There are also concerns among European health authorities for proposals to accelerate the introduction of new premium priced medicines – adaptive pathways – without adequate and accepted definitions of innovation and unmet need among all key stakeholder groups [19]. Having said this, a number of European countries base their discussions with pharmaceutical companies on the potential prices of new medicines on their perceived level of innovation versus current standards without necessarily stating the methodology used for defining the different levels of innovation [20]-[21]-[22]-[23]. Their deliberations are subsequently heavily scrutinized by pharmaceutical companies, but are usually endorsed [22]-[23]-[24].

2. Innovation

As defined by OECD [13] innovation is the implementation of a new or significantly improved product (good or service), or process, a new marketing method, or a new organizational method in business practice, workplace organization or in external relations [13]. Innovation is not necessarily a given from a creation or invention. Novelty implementation must reach the final commercial design to be characterized as an innovation. In addition, the search for a competitive differential is essential to define what an innovation is. Consequently, an innovation is compounded by the application of what is new, aiming to seek competitive differentials from current treatment approaches in the case of new medicines.

It is interesting to highlight that innovative activities are fundamental forces for the introduction of competitive differentials. According to Kurz [25], producers are encouraged to introduce new methods, new types or products in order to move away from competitors in certain markets. Conforming to this [25], competition means rivalry in which only the successful innovators will survive. Consequently, the ability to innovate is essential to maintain competitive advantage and for the survival of modern corporations [26].

Kim and Lui [27] emphasize that innovation has been considered as one of the most important factors in strengthening companies' competitiveness. The highlight for an innovative company is the development of new products with a high innovation load, which forces the discontinuity of other products, i.e. disinvestment in these [28], or their reduced use. Alternatively, providing an improved attribute such as improved quality of care leading to an improved financial result.

As a result, improving the performance of a pharmaceutical company through gaining a competitive advantage, or keeping this advantage, is the goal of launching new products. This can be achieved, for example, with innovations that provide new products, new uses or combinations, increased product quality, open new markets, as well as reduce unit production costs, purchase costs, distribution or transportation costs [13]-[29]. Innovation actions may vary from one implementer to another, because some can expend efforts on more significant innovations, and others could be interested only in developing what is common to the market but new to the implementer, providing more restricted competitive gains.

Evolutionary theories have sustained broad support for the theory of innovation; however, it is seen that in neoclassical doctrine a refinement of theories has been identified and postulated by the inclusion of approaches such as competition, games and decision making, besides traditional Schumpterian approaches, such as industrial evolution and transformation [26]-[30]. The search of an advantage by companies is essential for those with innovative characteristics, in addition to the motivation inherent to the entrepreneur to launch something very new to achieve success. Kenney [31] emphasizes and divides motivations into: i) financial success with high capital gains or corporate profits; and ii) the enormous desire to succeed and win.

According to Futia [32], the main incentive resulting from R&D activity by individual companies is the perspective of changing the structure of the market and gaining market power through successful and decisive innovations. Despite this, investment in innovation is a resource allocation that involves strategic evaluation allied to technological, market and competitive uncertainties [33].

Innovation has become fundamental to achieve prominence and even greater importance from global competition [34]-[35]. In view of this, we believe it is necessary to adapt to the definition of innovation, considering that innovation is the provision of a new goods or new service/process/methodology or improvements in existing ones, searching to obtain a result that gives prominence and a competitive advantage to pharmaceutical companies.

3. Methods

An exploratory research was carried out, highlighting certain phenomena and aspects that contribute to the understanding of the investigated background [36]. Searches were carried out in 4 databases: SCOPUS, PubMed, Web of Science and Science direct. Articles published up to 2015 were selected, including those available online in 2015 with publication scheduled for

2016, in English and Portuguese. Terms used in the searches were related to innovation. The main descriptors used were: novelties, innovation, innovator, innovation policy and innovation diffusion; and they were conjugated to the terms: marketing, processes, services, management, organization, administrative, pharmaceutical technology, pharmaceutical processes, pharmaceutical industry, pharmaceutical chemistry, pharmaceutical marketing and medicines. Using a qualitative approach, which according to Vieira and Moraes [37] provides a greater flexibility for theory's adaptation of the phenomenon to a structural model of classification, an innovation hierarchical profile was delineated. Information used in this study was collected to aid the design and relationships between terminologies, as well as to base definitions and classifications with actual examples of innovations in the pharmaceutical industry [38].

4. Innovation types and subtypes

4.1. TYPOLOGY

According to OECD [13], Joseph Schumpeter identified five types of innovation: introduction of new products, introduction of new processes or production methods, opening of new markets, development of new chain's supplies resources and creation of new market structure in industry [13]-[35]-[39]. In this context, it is perceived that innovation transposes to basically technological issues and incorporates non-technological characteristics [13]-[40]. As reported by Souto [29], it is possible to distinguish technological and non-technological innovations within different contexts. It means that is reasonable to consider them as two large dimensions [29]. Among them, conforming to figure 1, four types stand out, considering the "schupeterian" categories adapted [13]; which are: (i) Product Innovation; (ii) Process Innovation; (iii) Marketing innovation; (iv) Organizational innovation.

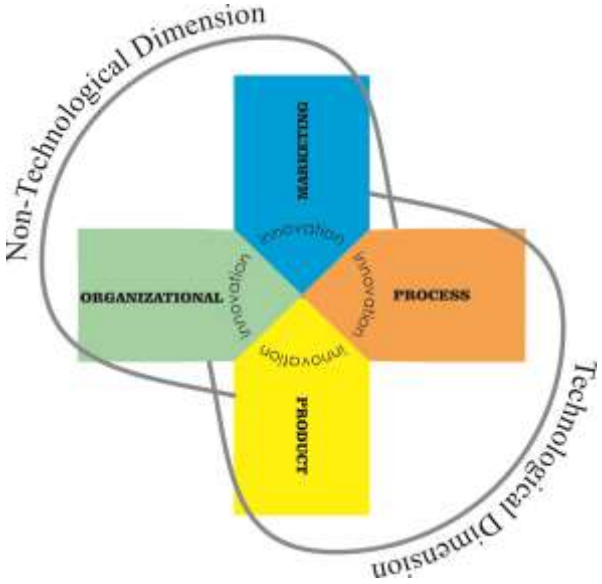

Figure 1: Representation of types of innovation integrated to technological and non-technological dimensions. Pentagons represent the dominance of innovation's types. The elliptical structure represents technological tendency or not of an innovation.

Product innovation is strongly, but not exclusively, linked to the concept of technological innovation. Product innovations may use new knowledge, technologies, or may be based on new uses or combinations of existing knowledge and technologies. These include the introduction of new products and significant improvements in functional or use characteristics of existing goods and services [13]. However, a new product for a company will not always be a new product on the market. There is the option for the company to develop new products for its portfolio, being a novelty for the company, but not for the market. This development can improve business performance [41].

In the pharmaceutical industrial segment, an example of such an innovation was introduction of monoclonal antibodies (mAbs). In 1975, Köner and Milstein [42] identified that it was possible to hybridize antibody-producing cells of diverse origins that could be provide specific medical products of importance. In 1986, the first monoclonal antibody, muromonab-CD3, was launched. It was approved for the prevention of liver transplant rejection [43]-[44]. Since then, the study of monoclonal antibodies as new therapeutic approaches has attracted considerable attention of the pharmaceutical industry, and these product innovations have been a considerable economic success [45]. For example, the utilization of the anti-TNF alpha medicines for use in rheumatoid arthritis has also grown appreciably in recent years in view of their effectiveness especially once concerns with their safety in routine clinical care had been addresses through registries [6]-[46]-[47]-[48]-[49].

In addition, thiazide diuretics have been, for a long time, first line treatment for hypertension [50]. However, in 1981, the angiotensin converting enzyme inhibitors (ACEIs) became available and endorsed in the management of hypertension, especially in patients with concomitant diabetes to help prevent nephropathy [51]-[52]. More recently, angiotensin receptor blockers (ARBs) have been launched to reduce troublesome coughing in a minority of patients, with their use increasing with the availability of generic ARBs [53]-[54].

Another innovation was the launch of the first medicine for the treatment of peptic ulcers, cimetidine, which act as a selective antagonist of histamine (H2) receptors. This aroused the interest of other pharmaceutical companies in developing other H2 antagonists, employing the strategy of molecular modification, resulting in products known as "*me too*" [55]. The concept *me too* is historically simple and powerful to portray therapeutic molecules with similar mechanisms of action of those consecrated substances in the market [56]. Similar products included ranitidine, famotidine and nizatidine. Despite these new molecules being original and chemically distinct, they have a similar action when compared to the first drug released and the therapeutic class establisher [56]. This was followed by the development of the proton pump inhibitors starting with omeprazole, which subsequently displaced the H2 antagonists and were again seen as an innovation [57]-[58]-[59]-[60]. Again, other companies followed suit with the originator developing a follow-on compound – esomeprazole - to help minimize the revenue loss following the patent loss of omeprazole. This is called 'evergreening strategies' [61].

Other important developments include antibiotics, although

concerns now with the lack of new therapies [62]-[63]-[64]-[65], as well as the development of new medicines to combat rejection following organ transplantation starting with cyclosporine, which has recently been shown to improve graft survival versus newer medicines such as tacrolimus [66]. More recently new medicines to combat hepatitis C have been developed offering the potential for a cure. However, concerns with their costs and potential budget impact, despite very low cost of goods, have impacted on their utilization [67]-[68]-[69].

Process innovation is defined as the introduction of new processes, operational procedures, equipment or resources that improve the performance of the method, production and distribution, as well as other methodologies or improvements of existing ones. Consequently, the implanted innovations, even in the form of optimization, are a way of reducing unit costs, production or delivery times, quality improvement, or to produce or distribute a new or significantly improved product. These types of innovations can confer differential competitiveness [13]. This type of innovation may also result in reduced inventories, scale change in economics, greater flexibility in the production line and minimization of infrastructure investments [70]. Consequently, new or optimized processes can be a corporate strategy to seek competitiveness, and this can be a central factor determining the success or failure of companies in long term [71]. An example of application of this typology is the process of obtaining erythropoietin, which has been optimized by going from the old batch manufacturing process in a bioreactor with controlled agitation to culture in semi-continuous perfusion in fluidized bed bioreactors, resulting in considerable productivity gains [72].

Marketing innovation is the implementation of an approach or monitoring method, improved or new, in the market. This can occur through significant changes in packaging design, product offerings, positioning, product promotion or pricing [13]. Results generated by this approach are aimed at improving customer needs or, as a way of positioning the brand or products to increase sales by opening new markets or by increasing commercial appeal such effervescent flavoured acetaminophen. This may include changes in packaging design, changes in marketing strategies, new media, credibility strengthening, and linking to welfare programs.

According to Becker and Lillemark [73] within pharmaceutical industry, the development of new medicines through R&D is common, which still persists today [6]-[74], combined with the delivery of these products to the market. Typically, marketing departments have considerable budgets in comparison to other departments [75], enhancing the profitability of the sector [76]. The 1990s were marked by the idea of increasing marketing integration with other industry areas, creating a trend in the sector. This multidisciplinary integration was new in the pharmaceutical sector and had as its main motivation the beneficial economic effects on the performance of new product launches [73]-[77].

According to OECD [13] a change in the form and appearance of the product/service without changing functional characteristics and use constitutes a marketing innovation. In this paper, this statement is divided into: i) if the change in appearance, for example, the introduction of the brand in low relief in pills, which will be understood as an innovation in marketing because it is the simple business differentiation or embellishment of the product; on the other hand, ii) when the change goes beyond appearance, it is considered that this change is a differentiation of the product itself. An example of the latter is the change of a vial to a filled syringe that facilitates delivery of the drug. Alternatively, the development of a longer acting injectable formulation resulting in once a day, once a week, or once a month, to improve compliance or the development of a longer acting injection from an oral formulation to improve compliance as seen with the antipsychotic medicines [78]-[79]. In this case, it's understood that those constitutes a product innovation. Novelties introduced regarding issues of storage and the supply chain, but that do not generate improvements in dosage such as packaging with markers that make it difficult for counterfeiters, or that make the packaging becomes more enticing, are also understood as marketing innovations.

Product's positioning through sales channels, billboards, magazines, advertising, television programs, internet media and other means of dissemination, even if subtle, can also be considered as new approaches, possibly characterized as marketing innovations. Another common strategy is to differentiate the price of medicines' brand and generic drugs by "value adding" to the brand [4] or to vary the price with the consumption as a result of the relation between demand and supply. This is more difficult with good quality generics with multiple publications showing no difference in effectiveness between the originator and generic across many drug classes, leading to for instance high voluntary International nonproprietary name (INN) prescribing in the UK [7]-[80]-[81]-[82]-[83].

Development and introduction of a new organizational procedure, not previously employed, is framed as organizational innovation [13]-[84]. This can cover several areas, such as financial, information technology, administrative, purchasing, and logistics, and should impart competitive differentiation related to increased performance or reduced operating costs. Camisón and Villar-López [85] emphasize what was evidenced by Hamel [86] that organizational innovation represents one of the most important and sustainable means of competitive advantage. The OECD [13] considers that other organizational changes, such as actions that improve workplace satisfaction with consequent productivity improvement, are also organizational innovations.

Organizational innovations also encompass methodologies that increase the level of learning and knowledge sharing in an embracing way. For example, the implementation of computer systems such as ERP (Enterprise Resource Planning) that manage facilities' production and stock. Initiatives that establish new approaches with suppliers that can result in simpler and faster procedures are, also, widely used as organizational changes.

Companies' mergers and acquisitions, common practice in the pharmaceutical segment as a competitive strategy, are also considered organizational innovations, but these may interfere with other forms of innovation such marketing. In this case, the framework is dependent on the main strategy for the merger. If the prevailing acquisition or merger strategy is to harmonize

organizational practices between two companies to give them greater competitive strength, acquiring technology or improved incorporating of a basket of products and processes, the main framework will be organizational. Although, if the reason is based on increasing marketing power, improving brand positioning, reliability or image, they are classified as a marketing innovation.

As an example of this type of innovation, was the hostile takeover of Warner-Lambert's by Pfizer [87]. According to Kipp and Leiding [88], this type of acquisition was advantageous because Pfizer was able to implement operational and staff decisions without major concerns with institutional culture as the companies had been previously co-promoted products including atorvastatin. Another example was the outsourcing of data centers and help desks to increase efficiency and a major concentration of the consumer's health field by AstraZeneca with IBM [88]. The pharmaceutical industry had improved e-business with this development, classifying this as an organizational innovation contributing to a marketing innovation [85].

4.2. SUBTYPE

Conceptually, according to Garcia and Calantone [12] new approaches are often classified in order to identify their innovative characteristics or the degree of innovation, with potentially 79 categories subdivided into five large groups. Denominations of each category differ in the form of understanding and according to the authors' interpretation. However, there is typically a lack of harmonization between authors regarding innovation typology.

Higgins [89] suggests three levels of innovation: i) incremental and continuous improvements; ii) significant improvements, where new products are developed from existing ones; or iii) "big bang" innovations that transform the way products or services are perceived or appropriated for consumption. According to Cooper [90] due to many definitions of innovation, it is now widely accepted that innovation can be expressed in a number of ways. The most prominent forms are defined as radical, incremental, product, process, administrative and technological innovations. Saaksjarvi [91], categorizes innovations into three large types: i) continuous, in which small modifications occur in current products; ii) continuous dynamic, where there is the creation of a new product or modification of the existing ones; iii) and discontinuous, in which there is the creation of a new product previously unknown that requires learning.

However, in our study, two distinct and sequential classifications (types and subtypes) are proposed and used. Our proposal is to first point out the type of innovation: product, process, marketing or organizational change and, subsequently, subcategorize these into subtypes, as shown in Figure 2. According to Sidin and Sham [92], there are three degrees of innovation, categorized as incremental, semi radicals and radicals. This contrasts with Garcia and Calantone [12] who suggest four types of innovation, i.e. radical innovation, really new, discontinuous and imitative. The classification emphasizes the degree of novelty involved, such as those that employ radical innovation at one end whilst imitative at the other, through incremental innovation or improvements. There is congruence among the innovation degrees' denominations highlighted by Sidin and Sham [92] and Garcia and Calantone [12] when discussing the pharmaceutical industry. Consequently, our proposed the subtypes are based on an adaptation of these two authors and include radical, semi-radical, incremental and imitative (Figure 2).

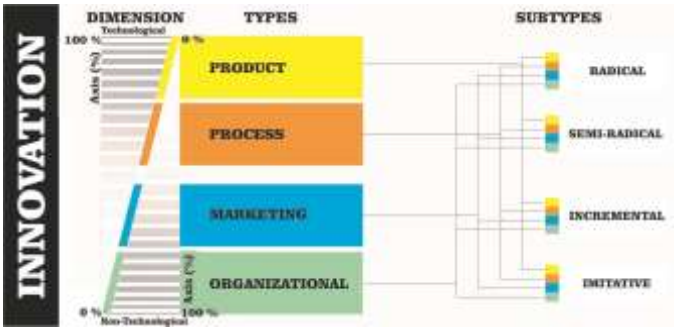

Figure 2: Layering of dimensions, innovation types and subtypes integrated.

4.2.1. Subtypes of product innovation

Radical innovations reformulate behavior and the current structure of a market [12]. This contrasts with the definition employed by Leifer et al. [93] who suggested that radical innovation is realized through unique or significant improvements in existing resources and improve cost and product performance. The concept of Vasconcelos [94] defines radical innovation as a totally new product, with characteristics quite distinct from previous products, which requires new skills among both providers and customers. Radical innovations should incorporate a new technology or knowledge that results in a new market infrastructure. Radical is characterized by extreme differences from what is considered traditional or usual, and should lead to existing products becoming obsolete, i.e. disinvestment.

Often though, radical novelties do not address a known requirement, but may create a demand previously unrecognized by the consumer. This new demand, for example, could be generated by the discovery of new medicines to address an unmet medical need, diseases that do not have available treatments, or through a pre-existing demand but with a new therapeutic approach that is considerably more effective or efficient resulting in substitution of current treatment approaches. A new drug that provides a preventive or curative effect is an excellent case of a radical innovation. Examples include vaccines against smallpox leading to the eradication of the disease [95]-[96]-[97], H2 antagonists appreciably reducing the need for operations for stomach ulcers and effectives cures for Hepatitis C [57]-[58]-[59]-[60]-[67]-[68]-[69].

Another example, more recently, of radical innovation in pharmaceutical market was a sildenafil in 1998. This new drug provided a breakthrough for sexual medicine with a refined clinical approach to sexual health disorder. Before the release of this drug, treatment was performed with invasive applications of injectable alprostadil [98]. Sildenafil provided intense displacement with significant substitution of the previous drug, as well as creating new clients who started treatment due to the ease of oral therapy. Monoclonal antibodies are another example [6]-[43]-[44]-[45]-[46]-[47]-

[48]-[49]. The selective serotonin re-uptake inhibitors (SSRIs) launched in 1987 are also an example as they helped to revolutionize the management of depression in ambulatory care [99]. Other examples include finasteride and tamoxifen in 1992 [60].

Garcia and Calantone [12] indicated that only 10% of all innovations fall into the category of radical innovations. In pharmaceutical industry, the proportion of radical innovations is now seen as even smaller [8]-[9]. Similarly, Kipp and Leiding [88] indicated that between 1989 and 1993, the Food and Drug Administration (FDA) approved 127 new molecular entities (excluding generic drugs), but only a minority offered a clear clinical advantage.

Less rare are semi-radical innovations which are seen as new items combined with a market novelty that generate competition and displacement, but not discontinuity of other products. Examples of this are "*me too*" medicines, chemically distinct, but with mechanisms of action similar to the initial medicines in the class or related class. Examples include different Proton Pump Inhibitors (PPIs) and the Angiotensin II Receptor Blockers (ARBs) [54]-[100]-[101]. Examples of radical and semi-radical innovations include the statins. Lovastatin was approved in 1987 for treatment of hypercholesterolemia, with simvastatin approved in 1991, atorvastatin approved in 1996 and rosuvastatin approved in 2003 [102]-[103]-[104]. Their appreciable impact on reducing coronary vascular (CV) events in high risk patients has resulted in their use in over 10% of some populations [101]. The advent of low cost generic atorvastatin is leading to recommendations in the UK to an appreciable increase in its dosing to further reduce CV morbidity and mortality [7]. Similar examples of radical and semi-radical innovations are the PPIs versus the H2 blockers [57]-[58]-[59]-[60] with again high consumption in some countries [101].

Despite this, there are many debates surrounding the essentiality of the "*me too*" therapeutic substances. Gagne and Choudhry [105] point out that market competition between similar drugs can reduce the cost of all drugs in the therapeutic class and improve accessibility for patients and healthcare systems. However, this is not typically the case and prices of medicines usually only decrease appreciably once there are generic products in a class coupled with reference pricing within the class [7]-[106]-[107]. In some cases, more options to prescribers may improve clinical outcomes since some medicines may have distinct efficiency or safety profiles for specific patients. This includes the anti-depressants and anti-psychotics where typically treatments are tailored to individual patients with limited guidance from health authorities unless there are concerns with the cost-effectiveness of patented medicines including formulations in routine clinical care once low cost generics are available in the class or disease area [108]-[109]. There were concerns with the value of duloxetine in Sweden due to appreciably higher prices than generic venlafaxine and mirtazapine but concerns with its effectiveness, leading to prescribing restrictions [110]. However, a "me too" can foster competition between companies reducing their market shares, which is a powerful stimulus for research and development of new substances of therapeutic interest [104] to maintain shareholder interest.

Insulin glargine, approved by FDA in 2000, is another potential case of semi-radical innovation. This medicine is the result of three modifications of human insulin produced by recombinant DNA technology [111]. However, there have been concerns with actual outcome differences between insulin glargine and NPH insulins, challenging the high prices for insulin glargine leading to calls to lower prices for continued reimbursement [112]-[113].

The incremental subtype covers products resulting from substitution or addition of a certain technical characteristic or necessary competence for the production or use of the product. In addition, resulting from a new specification of an already existing characteristic through an improvement in a product attribute without modifying the system as a whole [94]. The basic idea of this subtype is that the new medicine has improved properties leading to substitution of existing medicines over time. Vasconcelos [94] describes as an incremental concept the innovation by recombination, combining from different characteristics of products or new uses of existing products. These innovations have higher success rates with implementation and lower risks, effort and resources when compared to radical and semi-radical subtypes [92]. Some incremental innovations maybe so important that they can cause some market displacement, but they differ from semi-radical innovations because they are not entirely new, just modified. An example is the association of amoxicillin with clavulanate – co-amoxiclav [114].

Other examples include coatings applied to pharmaceutical forms to protect them in the stomach and reduce side-effects as well as controlled drug release system to reducing dosing and improve compliance [115]-[116]-[117].

The last innovation's subtype, the imitative one, has many definitions as it is difficult to find a common definition for this classification, since innovation and imitation are at opposite ends. The only common feature of the various definitions is that innovation implies novelty and imitation refers to replicating or doing the same [34]-[118].

In this paper, innovation is considered to be everything that is new to the company and which gives a competitive advantage in the market. In this way, an imitation is in general, the quickest and easiest way to develop a product, which can confer a strategic differential. When linked to creative potential, imitations are capable of continuous and permanent improvements. Copying can be an excellent way to enter the market and stimulate an innovation environment, considering that innovation from the past is the starting point for future innovations.

Imitations has been defined as the form of technological development that expands the existing set of knowledge base of the company, but not the world as a whole [34]-[164]-[165]. Imitations are, usually, low density novelties; however, they can provide appreciable influence in companies and countries that do not dominate a given technology. The imitative

innovation is not incremental innovation, as shown by Garcia and Calantone [12] reaffirmed by Yu et al [118]. It is, in fact, an imitation, but used as a way to advance industrially in items with a high technological load which is little dominated and widespread in the world. Consequently, imitative innovation is not a simple routine copy, since it must be aggregated with little diffused technologies.

Instead of visualizing antagonistic imitation and innovation, we suggest the existence of an interface between purist imitation, imitative innovation, and innovation (Figure 3). To develop this context, imitation tends to be a routine copy, with no appreciable processing knowledge by the company that executes it. Examples of "purist" copies of medicines are generics and biosimilars.

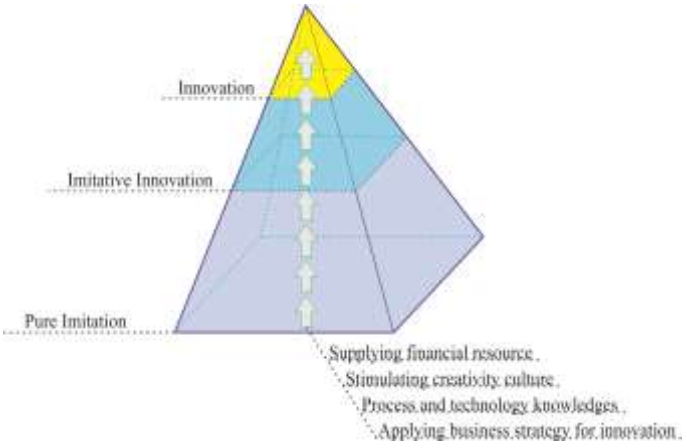

Figure 2: Pyramid of interface between purist imitation, imitative innovation and innovation. Arrows indicate the ascendancy and possible transposition of levels due to the technological knowledge, financial contribution, culture of stimulus to creativity, business strategy for innovation and methods and processes knowledges.

However, it is recognized that the development of biosimilars requires a higher degree of knowledge and technology versus small oral molecules [119]. Ongoing studies are also needed to help dispel myths regarding the effectiveness and safety of biosimilars versus originators [120]. The imitating action allows companies to change their position, gradually, through the strengthening of technological knowledge, and in a timely manner, having improved conditions and capacity to innovate. Yu and researchers [118] point out that China's innovative capacity has increased significantly since 2001, demonstrating the transition between innovative profiles.

With imitative practice, the company acquires manufacturing's know-how and, in the future, can perform incremental improvements in the product or process. Overall, imitative innovations have smallest risks of failure, since being a fast copier is a reliable strategy, with cost advantages and risk minimization [118]. Consequently, the imitative subtype innovation should not be underestimated as it may cause subdivision and displacement of markets, significantly altering their direction [12], with the first innovative company potentially suffering immediate economic impacts with imitation.

4.2.2. Subtypes of Process Innovation

Conceptually, the radical subtype of process innovation is very similar to that of product innovation, with the safeguard of being applied to methods, procedures and operations to obtain a result. A radical innovation of the manufacturing process is, usually, linked to a new product of the radical subtype, as in the case of insulin development. Initially, insulin was derived from swine, bovine or equine pancreas. In the late 1970s and early 1980s, researchers cloned the genes of Human Insulin and expressed it in Escherichia coli. Recombinant insulin has now become the main source of insulin [121]-[122] leading to discontinuation of animal pancreas products [121]-[123]. As mentioned earlier, the modification in the production of EPO is another generating industrial gain [72].

Another semi-radical process innovation was the introduction of direct compression for tablet production. As a result, wet production processes are slowly being replaced by direct compression to improve production efficiency [124]-[125]-[126]-[127]-[128]-[129].

The incremental category is resulting from the substitution or addition of a given technological resource, equipment or methodology that impacts on reducing costs, improves yields and one that is faster in obtaining the final product. In light of this, these new developments can be understood as creative measures to reduce production set-up times, to develop tool exchanges with quick coupling to speed the machine's adjustment time and to develop new procedures, methods and processes to streamline manufacturing to give greater production performance.

The increasing need for faster and more effective analytical methods for quality control employment has boosted research in this area with the consequent development of Ultra High Performance Liquid Chromatography (UHPLC) equipment. This equipment with advanced systems and technology in the pump, detector and automatic sampler represented an incremental innovation in the process of physical-chemical analysis [130]-[131].

Companies dedicated to develop new technology, such as bioprocesses, usually do not have access to original drug protocols of production, since such information is usually restricted. Consequently, in the case of biosimilars, manufacturing processes will be mixed, adding imitative and incremental steps to the origin process. For instance, infliximab CT-P13 was approved in 2013 by the European Medicines Agency (EMA) and, although it was developed to replicate with great accuracy the original product, there are minor distinctions in manufacturing steps in the production line and in the manufacturing process [132]-[133]-[134]-[135].

4.2.3. Subtypes of marketing innovation

Considering the definitions of Kotler and Armstrong [136], the main task of marketing is "to achieve profitable growth for the company" [137]. Consequently, marketing groups must be able to identify, evaluate and select market opportunities, in addition to formulating strategies to capture these opportunities. Marketing among pharmaceutical companies is often regulated by public sector through restricted access to physicians and the nature of information disseminated to physicians given current

concerns [138]-[139]-[140]. In some cases, abuse can lead to fines as well as negatively impacting on future reimbursement negotiations [141]. Other mechanisms include advertising in magazines and congresses, lobbying, sponsoring physicians to attend congresses as well as direct payments to physicians [142]-[143]-[144].

The use of the internet for information and even for direct sales to consumers can be seen as a marketing radical innovation. The internet benefits individuals who could feel constrained and, through anonymity, privacy and convenience that the internet provides, users can obtain information about symptoms and be motivated to seek medical help [145]. The internet can also be used by healthcare providers to stimulate improved management of patients with non-communicable diseases especially where adherence to lifestyle changes and medicine use is a concern [146].

The Internet can also be used as a potent information and sales tool to promote the use of medicines. However, many authors express concern about the "cyberchondriacs" generation [145]. There are also concerns where companies are now offering services to assess the genetic profile of patients but without sufficient evidence to support the findings [147]. France has been one of the only countries to ban such activities [147]. The internet also brings facilities such as online pharmacies and sites known as "No Prescription Web Sites" (NPWs) where it is possible to buy prescription drugs without prescription, which favors self-medication [145].

In a semi-radical approach, through direct marketing, there was a new polarization in pharmaceutical industry marketing by sending detailers to see physicians [148]. Pressures for increased return on investment in new therapeutic substances, or even financial return due to possible shortened life cycles, new marketing strategies, distribution and commercialization have now been employed. This includes direct to consumer advertising and building over-the-counter sales through the internet [148]. An example is the repositioning of terbinafine antifungal. A failure was reported in communication between physicians, who believed onychomycosis was more a cosmetic issue and did not take the disease seriously. Patients took this disease more seriously, but who were reluctant to discuss the matter with their physician. Faced with this, the pharmaceutical company redirected its campaign for greater awareness with advertisements to the consumer via the internet, highlighting the need for medical treatment, while medical advertising highlighted the concern of patients. This generated immediate results, increasing the sales [149].

The effervescent paracetamol tablet indicates an innovative action more about commercialization than product, since it is based on sales stimulation of sales due to the development of a faster when compared with oral tablets [150]. This repositioning is configured as an incremental innovation.

4.2.4. Subtypes of organizational innovation

Culture and organizational methods can also lead to improved economic performance when applied to quality, communication, information and learning. Management measures can make the organization more effective and efficient. Development of radical tools and methods in an organization can considerably influence efficiency in management and financial returns for the company. Organizational innovations are based on new methods' creation within the organization that provide an application for new knowledge, skills, devices and instruments to better target, measure, encourage and monitor actions, in order to make the organization more competitive.

In the past, pharmaceutical companies were dedicated more to improve patients' lives but ate the same time, generate profit to meet shareholders' needs and fund new research. However, their philosophy has undergone a significant cultural change over time. This ideological shift, demonstrated by the responsibility of increasing profits and investor returns, has directly impacted on corporate culture, with this goal now seen as essential [151]. This is seen by Kessel [151] who now argues that "medicine's ethics from the industrial pharmaceutical point of view has been replaced by the ethics of successful business". The supreme loyalty of corporations is now not primarily directed at patients and their doctors, but at shareholders. The adjustment of the traditional business model away from trying to improve patients' lives has suffered from shareholders' pressure to intensify financial results.

In this scenario, patients' needs became secondary due the business emphasis, because companies are measured on how well their actions are negotiated and, as a consequence, administrative councils encourage this approach as a way to improve return on the investment [151]. This cultural change can be classified as a radical organizational novelty, since it deconstituted the previous cultural practice to concentrate on this one, essentially, leading to more prominent financial results through managerial practices. One example is the pricing of new cures for Hepatitis C where the cost-of-goods accounted for less than 0.1% of the initial price request leading to appreciable concerns of affordability across counties [67]-[68]-[69]. Another example is the intense pressure now being placed on countries to fund new very expensive medicines in emotive disease areas such as cancer and orphan diseases with very little health gain [15]-[16]-[152]-[153]. As a result, patients with other diseases lose out within healthcare systems that seek to provide universal healthcare within finite resources.

Validation in pharmaceutical industry can be characterized as a novel semi-radical organizational technique with the objective of demonstrating the reliability of procedures and processes in medicines' manufacture. The concept of validation was introduced by two FDA staff members in the mid-1970s, to reduce errors and quality deviations [154]. This was a novelty that established the standardization of how to demonstrate robustness in drug manufacturing practices.

Another successful example of organizational change occurred in the 1940s, when Toyota, a Japanese automaker, developed and pioneered the application of the Lean concept, basing its performance model on a continuous flow [155]. The methodology was revolutionary and, therefore, radical in the automotive industry, changing the way the supply chain operates, how decisions are made and how people position themselves professionally. The Lean concept is mainly composed of the "just in time" system, which seeks a way to stabilize the production process and avoid overproduction [155]-[156]. The same principles have been applied to the pharmaceutical industry as an example of an imitative novelty already performed in other industries. Although the application has been similar to the system developed by the Japanese automobile segment, the methodology and the way of execution

can be adapted to the particularities of pharmaceutical segment with employment in different contexts and conferring a competitive advantage on companies that implemented it. These adaptations should be understood as incremental innovations.

5. DISCUSSION AND CONCLUSION

Innovation is widely employed in different context among pharmaceutical companies. However, their vast diversity makes it difficult to classify them. The inconsistencies in the framing and confusions with the application of the different terms used for classifying innovations may have contributed to the slow progression of knowledge and comparisons in these areas. Little has been published to date evaluating pharmaceutical innovations and their economic impact within the different classification factors of innovation. This study developed and analyzed the different potential innovation profiles among pharmaceutical companies from the types and subtypes of innovation.

This involved the fusion of different classifications already delineated in the literature rather than the generation of new terms, exemplified by existing cases and techniques. In addition, profile stratification was created, which can be used for future frameworks and to fill this void, as well as to make a more didactic the identification of different innovative or imitative behaviors among pharmaceutical companies. The conceptual domain and its definitions are the key to contrast and compare different types of innovations.

Radical and semi-radical innovations have the potential to offer appreciable profits and competitive advantage, but, in return, they require high risk, as well as potentially considerable company effort and resources [92]. Set as potentially risky items for the business, since not all innovation projects are successful and many investments may be lost due to innovation failure. This is especially evidenced in the pharmaceutical industry. However, risks are reduced by basic R & D being increasingly undertaken by universities, often with public monies. Some authors have estimated that over 80% of all basic research leading to new medicines is now undertaken by non-profit, university affiliated centres [157]. In addition, the cost of producing a new medicine is increasingly seen as nearer US$100 million rather than the often quoted figure of US$2.6billion [18]-[76]-[158].

Pharmaceutical companies generally apply considerable R&D investments for radical and semi-radical innovations, especially for new medicines. The technological innovation can be extremely expensive and it can take a long time for new medicines to be introduced into the market given the increasing safety and other tests that now have to be performed for companies to receive a marketing authorization [159]. The failure rate in pharmaceutical R&D for new therapeutic molecules is high. According to Mazzucato and Tancioni [159], about 1 in 10 thousand chemical compounds reach the market. However, the increasing use of universities to undertake basic research may help to reduce this. In addition to the risk of failure due to possible deficiencies of their own innovation, there are other failures, such as the use, or innovation provider [160] that have a direct impact on a product's success.

However, not all innovations are radical or semi-radical. Many are incremental and more process oriented. Hellwing [161] studying the competitive strategies of American and Japanese companies saw that Japanese companies are more concerned with incremental innovations, in learning from failures and focusing on productive process. Americans companies on the other hand were more concerned with novelty and radical innovations capable of discontinuing other products in the market place [162]. Companies that innovate successfully thrive at the expense of their less able competitors. That is why innovation is so fundamental to manufacturing industries, to their surviving and maintenance of market competitiveness. This is even more important with, as mentioned, an appreciable number of standard medicines are now available as low cost generics or biosimilars [7].

Allen and Hamilton [163] showed that less than 10% of innovations were new to the world. Barbieri [162] believed that about two-thirds of innovations have a small impact and cost less than US $ 100,000.00. However, they contribute significantly to commercial success. Most of innovations were improvements, additions to existing products, repositioning of the product and cost reduction by replacing an input with another that serve the same purpose. So, smaller innovations should not be look down upon since they can promote efficiency and effectiveness, including how well the products were manufactured in accordance to specifications and how those specifications reflect what customers really value.

Allied to creativity, imitations are a great source of improvement, from mastering the methods of obtaining the product or service. Evaluating an imitative innovation implies a distortion of technological dominance and continuous evolution. In this case, our conceptual proposal is that there are interfaces between pure imitation, imitative innovation and innovation. Regarding the elucidated differences, the common factor in literature is the agreement that a copy can't be underestimated, since it can confer technological differential and provide a competitive advantage. Moreover, what makes the imitation attractive is the power that it can generate from technology knowledge and creation, product, process, marketing, and organizational skills. According to Yu and researchers [118] "original innovation is the magic key for making success, and imitation is just the first stage". Consequently, in this point of view, imitative innovation is the way to promote and make technological diffusion in companies and in the world.

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