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The Driving Force of Exaptation and Its Implications for Innovation: An Empirical Analysis Based on the U.S. Pharmaceutical Industry

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Abstract

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Exaptation, a series of patterns that an emergent trait or function is coopted for a current usage which is completely different from the original usage, is a crucial component of novelty generation in innovation but has been underexplored so far. A few previous studies have scrutinized and analyzed the role of exaptation and its implications qualitatively, but most merely focus on an academic debate, which leaves a research gap in the practical field.

The study here thus analyzes the pattern of exaptation by measuring its frequency in the pharmaceutical industry through which ultimately captures its core driving forces as

an emergent mechanism of opportunity discovery in the real world. This process allows us to quantify the overall frequency of exaptation and demonstrate its origin with regards to the dual side of spaces of the possible: applicant-oriented and artifact-oriented. We observed that about 59% of emergent functions derived from the existing drugs stem from exaptation and about 30% of FDA-approved NMEs have an inherent exaptive nature. Furthermore, we found that firms' open innovation adoption and portfolio diversification strategy stand spaces of the possible as a powerful inducer of exaptation along with the popularity of drug classes and the initial versatility of drugs which compose the other side of spaces of the possible.

Based on its unique locus regarding the emergence of innovation, we propose that exaptation is one of the undeniable key attributes in innovation that can be structurally fostered, not via serendipity itself, which leads to innovation as an ex-post way of the exploration process.

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Chapter 1.   Introduction

1.1 Background

Considering Schumpeter's theory of technological innovation, evolutionary thinking, which dynamically stands for socioeconomic phenomena, provides a new interpretation for the principles of technological innovation emergence (Anderson & Tushman, 1986; Mokyr, 2016; Nelson, 2009; Tellis & Crawford, 1981; Wagner & Rosen, 2014). By borrowing the evolutionary principles of universal Darwinism (Cambell, 1960; Dawkins, 1983; McKelvey, 1997; Nelson & Winter, 1982; Plotkin, 1997; Smolin, 1997), various studies have attempted to derive a series of common patterns of ex-post phenomena in technological innovation and interpreted each as a stylized fact of the emergence of such innovation, thereby providing the main logic for predicting future innovations (Audretsch & Mahmood, 1994; Hausmann & Klinger, 2007; Klette & Kortum, 2004; Lööf & Heshmati, 2006; McKelvey, Rickne & Laage-Hellman, 2004; Peretto, 1998; Salter & Alexy, 2014). In particular, several studies have scrutinized the novelty generation process, which is one of the prerequisites for technological innovation, and "exaptation" is a prime example of this (Andriani & Cattani. 2016; Andriani & Kaminska, 2021; Cattani, 2006; Dew et al., 2004; Frigotto & Palmi, 2020; Ganfornina & Sánchez, 1999; Kauffman, 2000).

Exaptation is a series of patterns that an emergent trait or function is coopted for a current usage, completely different from its existing usage (Gould & Vrba, 1982).

There are many anecdotal examples of exaptation. In biology, a bird's wing is the best example to understand this phenomenon. Originally, a bird's wing was a part of its circulatory system and helped efficiently regulate its body temperature. However, the wing's function has evolutionized and it is now used entirely as an organ for flying. Similarly, the spawning organ of bees, which is used for attacking invaders, and the sweat glands of mammals that transformed into mammary glands are observable examples of exaptation in nature. Exaptation occurs not only in nature but also in the field of technology. In fact, various innovative technologies and products that we currently use are results of exaptation. For example, Viagra by Pfizer was developed as a treatment for pulmonary cardiovascular hypertension. However, an unexpected side effect was discovered during clinical trials for its approval, and the drug is now being used for erectile dysfunction treatment; thus, it has exapted from its original usage. Due to its effectiveness and portability, Viagra is considered a drug that led to innovation in the field of urology. Further, the first antidepressant, Marsilid, which was originally developed to treat tuberculosis, was also exapted after some patients felt euphoria after taking the pills. In addition, microwaves were invented through exaptation. In 1945, a researcher named Percy Spencer, who was working as a U.S. military contractor observed that his candy melted when he was in the vicinity of a radar, and discovered that a specific vacuum tube called magnetron causes this phenomenon. This accidental event led to the invention of microwaves. Therefore, microwave appliances were exapted from military radar technology. The discovery of microwaves is considered the second significant innovation

in cooking after the discovery of fire.

These anecdotal examples clearly show the importance of exaptation in the emergence of innovation as a way of novelty generation. Despite its importance, however, it has remained underexplored thus far, and most of the existing studies merely have focused on the ex-post implications of academic arguments without empirical approaches. Exaptation is not free from the limitation that its occurrence depends on serendipity, which cannot be structurally fostered. Therefore, despite its numerous implications as a crucial component to initiate innovation, the discussion of exaptation still remains at the theoretical level. Given this research gap, this study focuses on the empirical analysis of the phenomenon through qualitative approaches rather than anecdotal arguments of the concept itself. Therefore, analyzing the pharmaceutical industry, (1) we measure the frequency of exaptation in the real world, through which, (2) by tracing the fundamental driving forces of exaptation, we propose that exaptation is a key attribute in innovation that can be structurally fostered. We aim to re-illuminate exaptation from a balanced perspective by eliminating the existing biased myths and limitations.

This paper is structured as follows. Chapter 2 reviews the implications of exaptation for technological innovation and the theoretical backgrounds of spaces of the possible and open innovation necessary for demonstrating its driving force. Chapter 3 presents the frequency of exaptation by analyzing the pharmaceutical industry in the U.S. Chapter 4 proposes the hypothesis of this study and identifies the

driving force of exaptation. Finally, we describe the summary and implications of our

research in Chapter 5.

Chapter 2.   Literature Review

2.1 Exaptation

The term exaptation derived its concept from C. R. Darwin's evolution theory and was coined by Gould and Vrba (1982). Exaptation refers to "characters, evolved for other usages (or for no function at all), later coopted for their current role" (Gould & Vrba, 1982). In contrast, adaptation refers to "any characteristic of living organisms, which, in the environment they inhabit, improves their chances of survival, ultimately leaving descendants, in comparison with the chances of similar organisms without the characteristic" (Abercrombie et al., 1961; Bock, 1979). Thus, adaptation would mean the best survival strategy for each individual to find optimal fitness under the environmental selection pressure it faces. In this respect, exaptation, expressed as an accidental discovery of new functions for existing traits, is different from adaptation, which is defined as an improvement of traits through natural selection (Andriani & Carignani, 2014). Consequently, exaptation inherently implies a mutual dichotomy with adaptation.

Character	Process
Adaptation	Natural selection shapes the charcter for a current use - Adaptation
Exaptation	A character, previously shaped by natural selection for a particular function (an adaptation), is coopted for a new use - Cooptation
	A character whose origin cannot be ascribed to the direct action of natural selection (a nonaptation), is coopted for a current use - Cooptation

Table 1. Taxonomy of Fitness (Gould & Vrba, 1982)

Based on this idea, exaptation can explain various research gaps in the field of technological innovation as well as the survival strategies of individuals in nature (Andriani & Cattani, 2016; Cattani, 2006; Dew et al., 2004). It can be categorized into three main characteristics.

1. A stylized fact that latent functionalities are discovered by serendipity, which leads to the market niche in a new domain
2. A retrospective problem-solving process that finds a novel problem from an unexpected solution
3. A gear that connects radical and incremental innovation

Fundamentally and originally from an analogy, exaptation is a stylized fact that describes a series of patterns where technology or knowledge developed for a specific purpose is utilized in a new area with a function different from the existing one (Andriani & Carignani, 2014; Cattani, 2006; Mokyr, 1998). In this sense, exaptation suggests the integrated point of view as the best interpretation to explain the unique aspect that drives a new market niche through the discovery of latent functionalities by serendipity (Andriani & Cohen, 2013; Andriani, Ali & Mastrogiorgio, 2017; Beltagui et al., 2020; Dew & Sarasvathy, 2016; Garud, Gehman & Giuliani, 2018; Ganzaroli & Pilotti, 2010; Laland, Odling-Smee & Myles, 2010; Odling-Smee, Laland & Feldman, 2003; Venkataraman et al., 2012).

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Next, exaptation provides a completely different problem-solving process from what we have known. Traditionally, the problem-solving process has been based entirely on known scientific theories or market characteristics in which solutions were found. In that scenario, finding a solution to a novel problem is derived from the cognitive ability to infer the possibility of a solution from the given information (Felin & Zenger, 2016; Gavetti, 2012). That is, based on prior information, solutions are pulled from novel problems. Meanwhile, exaptation stems from the ability to recognize the potential of new uses within existing inertia, not from the cognitive ability to intentionally search for answers to novel problems through analogy (Mastrogiorgio & Mastrogiorgio, 2020). Accordingly, exapted results in a new situation apply the solution itself to the specific problem, which stands for the retrospective position that unexpected solutions drive novel problems. In other words, newly recognized problems originate from ex-post solutions of exaptation (von Hippel & von Krogh, 2016; Winter, 2012). Therefore, exaptation fills methodological gaps that could not be solved by the existing problem-solving process, thereby presenting a meaningful alternative from the opposite position (Andriani et al., 2017; Andriani & Kaminska, 2021).

__Exaptation__ concentrates on being retrospective position through which unexpected ex-post solution elicits the emergence of novel problem

__Exaptive solution → Novel problem__

Figure 1. Problem-Solving Process of Exaptation (Andriani & Kaminska, 2021)

Lastly, exaptation connects two innovation pathways in the emergence of innovation, that is, incremental innovation and radical innovation (Andriani & Carignani, 2014; Coccia, 2012). The opposite position of the problem-solving process leads to a paradigm shift that is completely different from the previous one. As is evident in the examples of Viagra and Marsilid, exaptation never originates from the improvement of original functions. Rather, it implies a functional shift process where latent functions are expressed in a completely different context; consequently, new uses, different from the original ones, emerge. In this regard, paradigm changes resulting from exaptation bear the characteristics of radical innovation simultaneously in terms of the scope and speed of its expansion, unlike adaptation that only leads incremental innovation where the existing technology and knowledge gradually expands (Andriani et al., 2017; Andriani & Kaminska, 2021). When such radical innovations interact with the market continuously and are maintained by repeating the self-reinforcing process of adaptation (Jacobs, 1969, 1985, 2000), the meaning of exaptation can be achieved. Therefore, by repeating a series of phenomena of temporal discovery and continuous adaptation regarding latent functionalities (Andriani & Carignani, 2014: avalanches of adaptive/exaptive responses, Levinthal, 1998: exaptive-adaptive cycle, Lane, 2011: exaptive bootstrapping), exaptation plays the role of a gear wheel that spurs radical and incremental innovation (Lane, 2011; Levinthal, 1998).

Since exaptation pays close attention to functional shifts, it is easy to misjudge all types of ex-post functional change observed as exaptation. For example, let us say that a

cell phone was used to crush peanut shells. We can see that the cell phone, a "mobile communication device," was utilized in a completely different way, that is, as a "crushing device" for crushing peanut shells. Thus, we can say that exaptation of the mobile phone has occurred due to the change of its function. Likewise, let us say that a towel was used to prevent suffocation during an emergency. This means that the towel was used as a "mask" to protect the respiratory system from toxic gas exposure, rather than "wiping something," and with the same logic mentioned before, we can say that exaptation has occurred. However, a functional shift is not merely a sufficient condition but a necessary condition for exaptation. This is because exaptation requires a functional shift that drives market demand in a new area and therefore makes continuous retention of the emergent function; in the absence of this, we cannot say exaptation has occurred (Andriani & Carignani, 2014). Hence, exaptation is not a temporal improvisation that only uses the original function differently according to the given situation (Tenner, 2004), but the evolutionary principle that follows the Variation-Selection-Retention (VSR) mechanism of universal Darwinism within the environmental selection pressure represented by the market.

2.2 Spaces of the possible

Spaces of the possible are the fundamental spaces where biological and technological evolution occur. Established by Wagner and Rosen (2014), spaces of the possible explore the emergent factors of innovation in the field of technology as an analogy of the

evolutionary principle in nature. The central dogma of molecular biology refers to the sequential information transfer process as the basic principle of all life phenomena in nature. According to this concept, genetic information is replicated and encoded by DNA, transferred to RNA by the transcription process, and then transferred again to protein by the translation process for its expression (Crick, 1970). The letters in the transmission and expression of genetic information are amino acids. Depending on the combination, 20 amino acids constitute the base of nucleic acids such as DNA and RNA as well as the sequence of proteins. In this respect, amino acid sequences or protein genotypes are the fundamental sources of all life phenomena (Smith, 1970). For the same reason, a genotype space comprising all possible combinations of these letters is the fundamental source space of all life phenomena, that is, a space of the possibilities of nature (Wagner & Rosen, 2014). In the field of technology, a space of possibilities is analogous to discovery, innovation, or design space (Stankiewicz, 2010). Further, as in the case of nature, it is also a fundamental source space for technological innovation. As the space of possible has been discussed with the central dogma of molecular biology in nature, the technological field has also attempted to identify its central principle historically. It dates back to the 18th century industrialist Christopher Polhem's case of the mechanical alphabet. He claimed that the mechanical alphabet such as a tiny lever or a screw could create a machine. Therefore, any kind of machine can be created by combining them (Strandh, 1988). In addition, a variety of discussions have suggested that the emergence of a technology or product is possible based on the modularity it bears (Andriani &

Carignani, 2014; Baldwin et al., 2000; Langlois, 2002; Sanchez & Mahoney, 1996; Schlosser & Wagner, 2004; Sturgeon, 2002; Ulrich, 1994).

In sum, a space of the possible is a space where various combinations and linkages between the basic letters that make up space can be made to acquire the basic principles of emergence. In this sense, the components (the basic letters) and the method of combination or linkage between them are the two most important aspects that should be considered in a space of the possible. In the case of nature, since 20 letters are involved in both the construction of nucleic acids and proteins as a component, the possibilities of amino acids in the birth or evolution of species are infinite. However, since the diversity of principles regarding combination and linkage is fairly limited, nature tries to constantly repeat trials and errors in an infinite amount of time called massive parallelism to overcome the given limitation (Wagner & Rosen, 2014; Ziman, 2000). The difference between biological and technological evolution is that, in the latter, the direction of evolution can be intentionally set based on the teleology (Kim, 2015; Ziman, 2003). In other words, unlike the case of nature, we can intentionally induce the emergence of technological innovation, which is in line with Schumpeter's argument (1934) regarding "carrying out of new combinations" (Edgerton, 2008; Hargardon, 2003; Kogut & Zander, 1992; Salter & Alexy, 2014). If we recall the core aspect of spaces of the possible, that is, the components and the method of combination or linkage between them, we can see that inducing the emergence of innovation cannot be different from enhancing the possibilities of these two factors. In this respect, we can denote the possibility of the emergence of

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innovation based on the modularity of the components and the diversity of the combination and linkage method as follows.

$$P_{Innovation} \propto (Modularity\ of\ Component)\ x\ (Diversity\ of\ Linkage)$$

(1)

A difference between the two key factors in the emergence of innovation is whether the inventor's will can be or cannot be involved in determining the extent of each factor. Specifically, the modularity of a component is an inherently given value regardless of the inventor's will. Conversely, improving the diversity of the combination or the linkage between components is a part in which the inventor's will can intervene in the emergence of innovation. Hence, a space of the possible consists of the area where the inventor's will can and cannot intervene.

In this sense, exaptation is the key principle of emergence regarding spaces of the possible along with combinatorial innovation as described in Wager and Rosen (2014). Exaptation stems from the combination of the existing usage of technology or products with new contextual factors that are directly related to the two key factors of spaces of the possible. An existing technology or product refers to a component of spaces of the possible, and the possibility of exaptation relies on the modularity of itself. Similarly, new contextual factors refer to the combination and linkage between components in spaces of the possible, and those diversities determine the possibility of exaptation. This is fundamentally in line with the main argument of Andriani and Carignani (2014), that is,

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modular exaptation, and is also consistent with the argument of Andriani and Cohen (2013) that the emergence of exaptation depends on the characteristics of the form–function phase space based on diversity and connectivity. Thus, we can also denote the possibility of exaptation as follows according to (1).

$$P_{Exaptation} \propto (Modularity\ of\ Artefact)\ x\ (Diversity\ of\ Contextuality)$$

(2)

2.3 Open Innovation

Open innovation refers to "a paradigm that assumes that firms can and should use external ideas as well as internal ideas, and internal and external paths to market, as they look to advance their technology" (Chesbrough, Vanhaverbeke & West, 2006). These newer models of innovation have highlighted the interactive character of the innovation process, suggesting that innovators rely heavily on their interaction with lead users, suppliers, and a range of institutions within the innovation system (Brown & Eisenhardt, 1955; Lundvall, 1992; Szulanski, 1996; von Hippel, 1988). The modern market environment shows great complexity as compared to the past, and it is no exaggeration to say that the high-tech industry is at the apex of this market. Large-scale investments required for massive production and collaboration with several strangers are inevitable for market operation (Bae, 2013). Open innovation encompasses various sub-concepts in that it refers to all processes in which a firm integrates and utilizes internal resources and

capabilities with external ones to sustain its competitive advantage in the market. In other words, open innovation endogenously assumes that the firm's resources and capabilities depend on the boundaries of the firm. Therefore, we need to first scrutinize the resource-based theory and the transaction cost theory. Based on the resource-based theory, firms' Valuable, Rare, Inimitable, and Non-substitutable (VRIN) resources can provide competitive advantages in the market (Barney, 1991). In this regard, firms strive to perpetuate their survival and sustain competitive advantages by utilizing and expanding their unique valuable resources. However, since all the resources cannot be ascribed to the VRIN resources that could enhance their competitive advantages, firms try to protect their core competence, while simultaneously complementarily leveraging external channels such as outsourcing the non-core competency (Lee, Park & Cho, 2012). Therefore, from the resource-based theory viewpoint, firms strive to maximize their competitive advantages based on internal resources while actively utilizing external resources to secure VRIN resources simultaneously. This in turn drives open innovation as an incentive.

Further, the transaction cost resulting from frictionness between the firm's decision and action can be minimized by arbitrarily adjusting the allocation of resources to the other party through an employment contract (Williamson, 1985). Therefore, firms try to compare and evaluate all transaction costs that may occur in the future in terms of private ordering and governance in advance. In addition, they are willing to find the most optimal organizational structure that can minimize transaction costs based on asset specificity,

uncertainty, and frequency. In other words, firms' actions would determine their boundaries in their market environment. That is, a firm sets the optimal boundary according to the market condition, considering its resources and transaction behavior (Afuah, 2001; Ahuja, 2000; Mariti & Smiley, 1983). In short, from the perspective of the transaction cost theory, a firm decides whether to internalize external resources into a single governance structure or to let them be supplemented using external channels based on the transaction cost (Baek & Noh, 2014). It can be said that it is related to the problem of choosing which strategy would be used to achieve open innovation.

As mentioned before, selecting and reconstructing the process of specific resources and knowledge cannot be separated from the improvement of firms' innovation performance. Thus, firms actively strive to maximize their capabilities based on their resource and knowledge pools since they can be rewarded in the form of profit maximization by securing competitive advantages and market shares. However, firms cannot acquire all the resources and knowledge that are necessary to enhance their innovation performance. They can also be ignorant as to which resources and knowledge could be directly related to innovation performance. This raises the need for information sharing. That is, we can access information that has blind spots and reconstruct the cornerstone for innovation by sharing resources and knowledge. Considering this, the process of sharing resources and knowledge as a way of open innovation can be interpreted as an exploration process. Therefore, we can regard it as a routine to perpetuate the firm's survival by reducing uncertainty (Nelson & Winter, 1982), and

consequently, it can be understood as a part of organizational learning that changes organizational behavior (Simon, 1945). Organizations should change their behavior to keep pace with the new circumstances, thereby to survive in the market. That is, the purpose of organizational change is to ensure organizations' survival; thus, the organizational problem-solving process, that is, organizational learning should be addressed. Hence, as a way of change management, exploration is the key concept for an organization to pursue. According to Pentland (2014), exploration refers to "the use of social networks in harvesting ideas and information in that it is the part of idea flow that brings new ideas into a workgroup or community." In the selection conflicts that may arise in this process, the results of others' searches serve as imitation pressure that triggers a specific choice, suggesting a complementary solution. Therefore, open innovation could be argued as an organizational learning process in which organizations, that is, firms, find the optimal boundaries based on their resources and capabilities to ensure and sustain their survival and competitive advantages. Accordingly, the process of resources and knowledge sharing between firms is most crucial and should be considered first for increasing firms' innovation performance. Therefore, we can say that the innovation performance of a firm through the reorganizing process of information relies on the inter-organizational relationship (Powell, Koput & Smith-doerr, 1996; Zander & Kogut, 1995).

Based on Chesbrough and Chen's (2013) argument, open innovation enables the identification of unexpected usages of drugs other than the current usages. This suggests that open innovation could increase the possibility of finding beneficial uses by

broadening the range of resources that can be recognized. In this case, open innovation is an exploration process in which firms could broaden their pool of resources and knowledge. It is a crucial strategy to expand the diversity of the combinations and linkages necessary for the emergence of innovation spaces of the possible. In other words, it is a strategic alternative to the part where the inventors' will can intervene to drive innovation. Considering the Eq. (2) in section 2.2, open innovation would be the best strategy that can structurally lead to the emergence of exaptation.

2.4 Research Question

As in section 2.2.1, qualitative research on exaptation in the academic field has been conducted from fairly diverse perspectives based on numerous anecdotal evidence. Analogous to evolutionary identity in nature, exaptation in the field of technological innovation has explained the research gap from three perspectives. Contrariwise, quantitative research on exaptation has been conducted at a very limited level. Andriani et al. (2017) measured the frequency of exaptation for New Molecular Entities (NMEs) in the pharmaceutical field and demonstrated the influence of exaptation on radical innovation in their study. However, it did not provide generalized implications; it used only 83 data samples, and the influence of exaptation on radical innovation was demonstrated by simple correlation without providing a clear standard. Furthermore, there has been no argument on the fundamental driving forces of exaptation. Consequently, although exaptation is a pivotal factor that should not be ignored in the

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emergence of innovation as the main attribute of novelty generation, it still depends on serendipitous luck; thus, the existing limitation is yet unresolved. Hence, exaptation does not provide any practical implications in the real world represented by markets and firms. Therefore, in this study, we empirically measure the frequency of exaptation and identify its fundamental driving forces by focusing on the quantitative aspect rather than the academic argument of the concept itself. In doing so, we propose that exaptation can be structurally fostered and does not merely emerge from serendipity.

Research Question: What is the driving force of exaptation and how can it be captured?

Step 1: Measuring the frequency of exaptation

Step 2: Identifying the origin of exaptation and capturing its driving force

Chapter 3.   Measuring the Frequency of Exaptation

3.1 The Pharmaceutical Industry

The pharmaceutical industry is appropriate for measuring exaptation for the following reasons (Andriani et al., 2017).

1. The artifacts, that is, drugs are identifiable and can be distinguished based on their unique characteristics.

2. The functions of the artifacts are systematized by the international database, and thus, can be classified.

3. Information of market needs, that is, diseases are systematized by international classification standards; thus, it is possible to identify how the indication of a drug for diseases has been expanding.

4. The emergence of new usages occurs easily whereas the initial approval of artifacts is heavily regulated; thus, it is easy to compare the emergent usage with the original usage.

Accordingly, in this study, we analyze the U.S. pharmaceutical industry to measure the frequency of exaptation. In the case of the U.S., the market entry of drugs is strictly regulated by the U.S. Food and Drug Administration (FDA), a federal agency responsible

for public health. Thereupon, only drugs that have passed all the regulations are approved as NMEs, resulting in what constitutes a high barrier to market entry. Therefore, NMEs that have been successfully approved by the FDA guarantee their efficacy, safety, and stability. Then, NMEs are exposed to contextual factors such as different physiological specificities of patients and concurrent diseases, which yield the non-approved usage of drugs, that is, the off-label usage (DeMonaco, Ali & von Hippel, 2006). In the U.S., doctors can prescribe drugs for off-label usages, whereas pharmaceutical companies banned such advertising other than for the approved usage of drugs (Ventola, 2009). On average, prescriptions for off-label usage account for 21% of the total. This goes up to 46% in the field of cardiac medications and anticonvulsants (Radley, Finkelstein & Stafford, 2006), and even 85% for pediatric chemotherapy (DeMonaco et al., 2006). Therefore, even though off-label usages have not been officially approved, we can say that their practical impact is enormous.

3.2 Empirical Setting

3.2.1   Sample

The sample here consists of FDA-approved molecular entity drugs, that is, NMEs, from 1998 to 2020 based on the U.S pharmaceutical market. We found that 733 NMEs were approved during this period. To scrutinize the original and emergent usage of drugs, the first step was to find credible information. Therefore, we used the FDA-official drug database along with the FDA annual drug calendars. We built our datasets using DrugDex

and Drugbank, which are one of the most widely used commercial databases for drug identification due to their availability and reliability (DeMonaco et al., 2006; Law et al., 2014; Tillman et al., 2009; Wishart et al., 2008). Additionally, we used Standard & Pool's Compustat, a widely-used database of financial and market information, to gather the financial information of the drug manufacturers (Chychyla & Kogan, 2015).

3.2.2 Measurement

From the perspective of dichotomous debate in the literature, it may be arbitrary to decide whether the emergence of new functions is derived from exaptation or adaptation since the line between them seems ambiguous. Even if the emergence of a new function drives the market demand in a new area, it is somewhat arduous to identify how new the function is compared to the original one. To attenuate these problems, the study measured the functional distance between the original and emergent usages of NMEs referring to Andriani et al. (2017). In this sense, both the original and emergent usages should be comparable within the same dimension, which is why a disease map is required. Hence, we used the International Classification of Diseases (ICD) established by the World Health Organization, which provides systematic disease information grouping based on the similarity of diseases. The U.S. modified the ICD to match their medical system; therefore, we used the latest modified version—the ICD-10-Clinical Modification (ICD-10-CM)—in this study. It classifies diseases according to their pathogenesis and anatomical position, using a tree structure. Specifically, diseases are categorized into 22

general classes and are then categorized into subclasses. Additionally, each subclass is further categorized into a more detailed one. Each disease is assigned a code consisting of an alphabet with two successive numbers, and, in some cases, two additional numbers are assigned to provide more detailed disease information (Fig. 2).
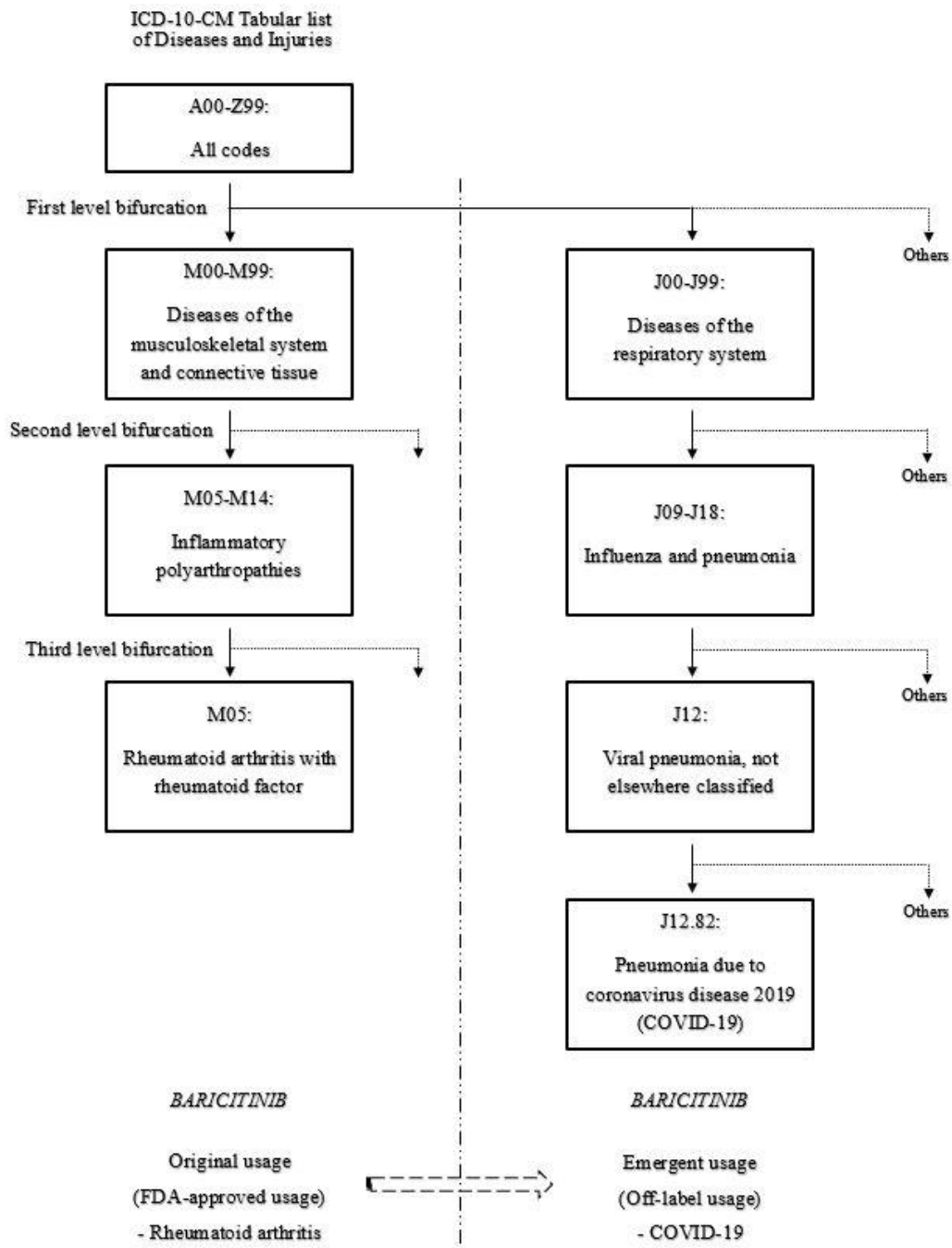
Figure 2. Distance on the ICD-10-CM

The distance between the original and emergent usage of an NME can be categorized into the following three based on the bifurcation point of the two usages in the ICD-10-CM.

A. Large distance: An NME's entry usage (original usage) and off-label usage (emergent usage) diverged at the general class, that is, a first-level bifurcation

B. Intermediate distance: An NME's entry usage (original usage) and off-label usage (emergent usage) diverged at the subclass, that is, a second level bifurcation

C. Short distance: An NME's entry usage (original usage) and off-label usage (emergent usage) have the same subclass but diverged at the lower level, that is, a third or lower-level bifurcation

Based on the distance above, the following logic steps are used to check the occurrence of exaptation.

1. For all NMEs, assign the ICD-10-CM code for all original usages and emergent usages based on each indication information.

2. Set each code of emergent usages as a starting point and then compare every combination that could have been made between the code of original usages and that of emergent usages.

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3. Find the shortest path and assign it as the distance of the emergent usage to determine the occurrence of exaptation.

4. If the distance from the original usage is large or intermediate, that is, bifurcated at the first or second level, consider it as the occurrence of exaptation.[1]

We can formulate this step as follows (Fig. 3).

For each NME,

❖   *Approved Usage* : $F_i = (\alpha_i, \beta_i, \gamma_i)^F \ for \ i = 1,2,3,\dots,l$

❖   *Emergent Usage* : $O_j = (\alpha_j, \beta_j, \gamma_j)^O \ for \ j = 1,2,3,\dots,m$
      # Each successive alpha-numeric indicating correspondent nested level in ICD-10-CM class

❖   *Distance : The shortest path among all sets of F_i and O_j wherein ICD-10-CM class*

$$\forall_i, min(F_i, O_j)$$

Weight : First bifurcation $\omega_1 = 1$, Second bifurcation $\omega_2 = 0$, Third bifurcation $\omega_3 = -1$

$$\alpha_j = \begin{cases} 1 \ (\alpha_i \neq \alpha_j) \\ 0 \ (\alpha_i = \alpha_j) \end{cases} \ same \ as \ with \ \beta \ and \ \gamma \ respectively$$

$$D_{F_i O_j} = \begin{cases} (\omega_1 \alpha_j + \omega_2 \beta_j + \omega_3 \gamma_j) \ (F_i \neq O_j) \\ \qquad\qquad -1 \qquad\qquad (F_i = O_j) \end{cases}$$

$$\therefore \ Emergent \ Usage = \begin{cases} Exaptation \ (D_{F_i O_j} \geq 0) \\ Adaptation \ (D_{F_i O_j} < 0) \end{cases}$$

Figure 3. Function of Exaptation

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[1] Bifurcation at the general or subclass level means that the market demand of the emergent usage does not conflict with that of the original usage. Conversely, if it is bifurcated at a much lower level, it may result in demand competition between usages within an overlapping market. Therefore, different market demand is the key factor in determining whether exaptation occurs or not.

For each NME, all the original and emergent usages can be substituted by a function with three successive values in the ICD-10-CM. A series of alpha, beta, and gamma refers to coordinates of a point considering each successive classification level. For example, in the case of BARICITINIB in Fig. 1, the original usage can be denoted as (13, 3, 1) and the emergent usage as (10, 2, 4); details can be found in Appendix. In addition, we value a different weight depending on the level of bifurcation between two usages. As discussed, the ICD-10-CM constitutes a tree structure where a general class has a different subclass that stands in a separate position. Hence, if the two usages have the same alpha value, that is, in the case of the first level bifurcation, it is meaningless to compare the beta and gamma. Likewise, if the two usages have the same alpha value but different beta, it is unnecessary to further compare the gamma value. In other words, we do not need to consider the subsection of the level where the bifurcation occurred. Assume that there are two usages with the coordinates of (13, 3, 1) and (12, 3, 2), respectively, in the ICD-10-CM. Since bifurcation has already occurred on the first level, it should be calculated as (1X1=1), not as [1X1+0X0+(-1)x(1)] by additionally considering the further subclass.

3.3 Results

For the total of 733 NMEs approved by the FDA from 1998 to 2020, we found that 1,090 emergent usages were newly generated out of 1,632 original usages. Among all emergent usages, exaptation occurred for 644 usages whereas adaptation occurred for 446 usages. Interestingly, in novelty generation, the impact of exaptation is greater than

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adaptation. This is clearly indicated in the case of NMEs approved by the FDA in 2004. The following is the cumulative distance of emergent usages in 2004 based on the logic of section 3.2.2 (Fig. 4).
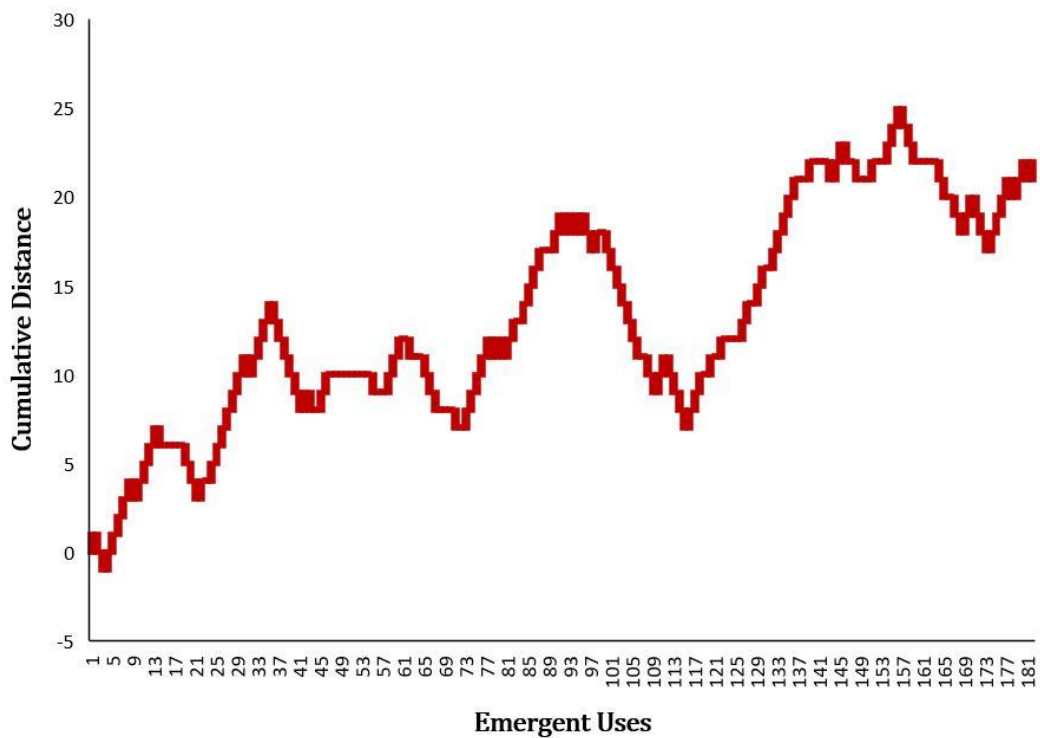
Figure 4. Cumulative Distance of Emergent Usages (2004)

In section 3.2.2, we stated that exaptation has occurred if the distance is positive, and adaptation has occurred if otherwise.[2] In this sense, for all NMEs approved by the FDA, even if the cumulative distance of emergent usages shows a value of 0 at the most, it

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[2] It takes a value of +1 for the first level bifurcation, 0 for the second level bifurcation, and -1 for the third or lower-level bifurcation. Thus, exaptation, which is defined as occurring at the first and second level bifurcation, has a positive value.

means that exaptation has more likely occurred than adaptation. Accordingly, the right upward result shown in Fig. 4 implies that exaptation has occurred at a higher rate than adaptation for NMEs approved by the FDA in 2004. We then revisualized this result to the realm of exaptation and adaptation based on each frequency (Fig. 5).
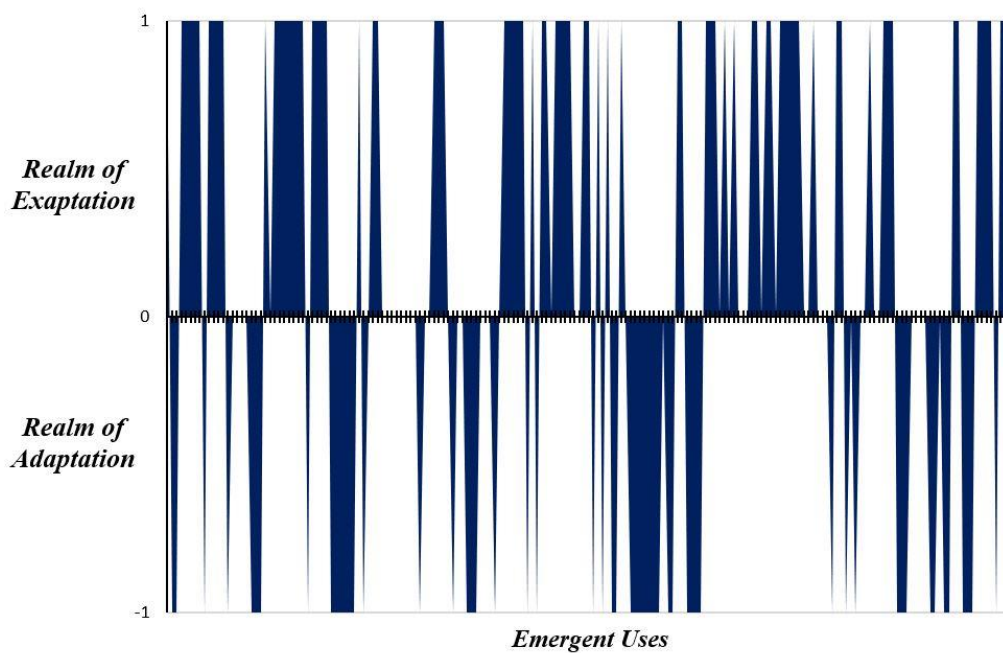
Figure 5. Realms of Exaptation and Adaptation (2004)

We observed that the realm of exaptation exceeded that of adaptation in Fig. 5, which is in line with the fact that exaptation has occurred more than adaptation.
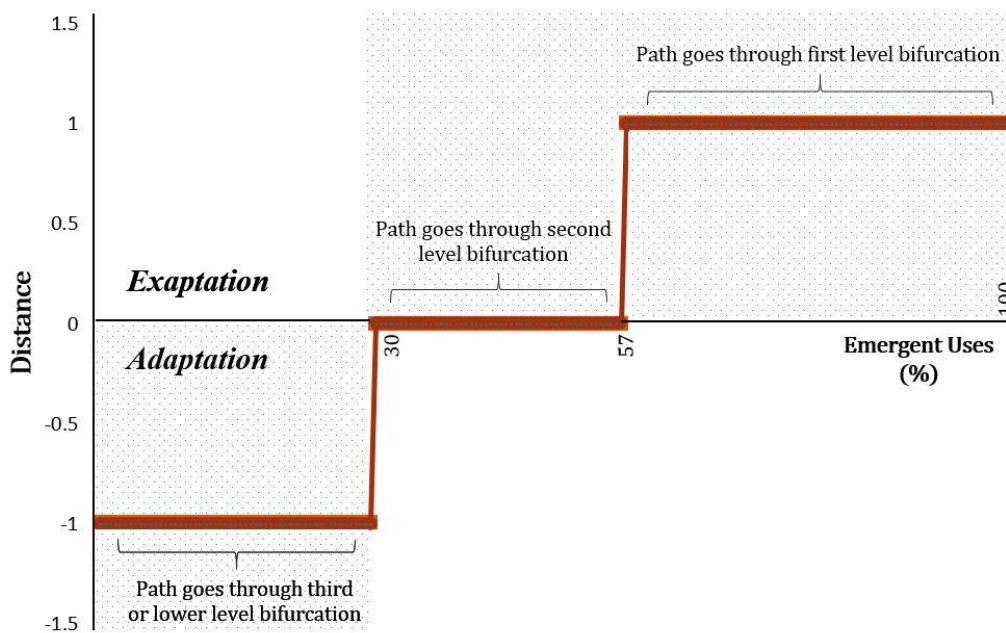
Figure 6. Ratio of Exaptation to Functional Emergence (2004)

Fig. 6 shows that exaptation accounts for as much as 70% in the emergence of new usages of NMEs approved by the FDA in 2004, that is, of the 182 emergent usages in 2004, 127 usages were from exaptation. Furthermore, it shows that exaptation has occurred more in the first level bifurcation than in the second. This means that the emergence of new functions tends to occur in a market that is much different from the market of existing usages. In other words, the expansion of the function occurs in far distinct areas radically rather than nearby areas of existing usages.

In this study, we termed the NME in which exaptation has occurred at least once as "Exapted Drug" and the NME that has recorded more exaptation than adaptation for all emergent usages as "Exaptive Drug," to identify the driving forces of exaptation in

chapter 4. Each was used as an indicator of whether exaptation occurred and its continual occurrence thereafter, respectively. We further denoted the "Tendency" of exaptation for all NMEs as a standard to statistically set the aforementioned.

$$Tendency = \frac{Exaptation}{Emergent\ Usage\ (Adaptation+Exaptation)}$$

(3)

Hence, exapted drugs have a positive value of tendency, and exaptive drugs have a value of tendency more than 0.5.

Exapted Drug : A drug that exaptation has occurred at least once (Tendency > 0)

Exaptive Drug : A drug that more exaptation occurred compared to adaptation (Tendency > 0.5)

(4)

We used the three variables above as dependent variables to explore the driving force of exaptation. Details will be discussed in chapter 4. The descriptive statistics are as follows (Table 2).

Variables	Description	Count	Mean	SD	Min.	Max.
Dependent Variable						
Tendency	Tendency to exaptation which stands for the ratio of exaptation to overall emergent usage, $\frac{Exaptation}{Emergent\ Usage\ (Adaptation+Exaptation)}$	733	0.231	0.382	0	1
Exapted Drug	A drug that exaptation has occurred at least once, $Tendency > 0$	733	0.300	0.459	0	1
Exaptive Drug	A drug that more exaptation has occurred compared to adaptation, $Tendency > 0.5$	733	0.214	0.382	0	1
N		733				
Group		206				

Table 2. Descriptive Statistics of Dependent Variables

The following are the main results of step 1, that is, measuring the frequency of exaptation for 733 NMEs approved by the FDA from 1998 to 2020.

Year	NMEs	Entry Uses	Emergent Uses	Adaptation	Exaptation	No Emergence	Exaptive Drug	Exapted Drug	Usage Emergence / NMEs	Entry Uses / NMEs	Emergent Uses / NMEs	Exaptation / Emergent Uses	Exaptation / All Uses	Exaptation / NMEs	Exaptive Drug / NMEs	Exapted Drug / NMEs
1998	30	61	118	36	82	6	15	19	80%	2.03	3.93	69%	46%	2.73	50%	63%
1999	35	78	106	40	66	6	15	20	83%	2.23	3.03	62%	36%	1.89	43%	57%
2000	27	54	75	31	44	3	11	20	89%	2.00	2.78	59%	34%	1.63	41%	74%
2001	24	79	48	29	19	6	6	10	75%	3.29	2.00	40%	15%	0.79	25%	42%
2002	17	41	68	29	39	2	8	11	88%	2.41	4.00	57%	36%	2.29	47%	65%
2003	21	42	64	24	40	5	9	12	76%	2.00	3.05	63%	38%	1.90	43%	57%
2004	36	89	182	55	127	5	21	26	86%	2.47	5.06	70%	47%	3.53	58%	72%
2005	20	46	60	23	37	8	7	11	60%	2.30	3.00	62%	35%	1.85	35%	55%
2006	22	45	56	26	30	9	7	10	59%	2.05	2.55	54%	30%	1.36	32%	45%
2007	18	31	37	13	24	5	7	9	72%	1.72	2.06	65%	35%	1.33	39%	50%
2008	24	41	22	8	14	11	8	9	54%	1.71	0.92	64%	22%	0.58	33%	38%
2009	26	70	44	16	28	12	7	10	54%	2.69	1.69	64%	25%	1.08	27%	38%
2010	21	55	29	12	17	9	6	9	57%	2.62	1.38	59%	20%	0.81	29%	43%
2011	30	72	41	21	20	14	6	8	53%	2.40	1.37	49%	18%	0.67	20%	27%
2012	39	75	43	22	21	25	4	7	36%	1.92	1.10	49%	18%	0.54	10%	18%
2013	29	91	18	12	6	17	3	5	41%	3.14	0.62	33%	6%	0.21	10%	17%
2014	41	153	28	17	11	24	6	9	41%	3.73	0.68	39%	6%	0.27	15%	22%
2015	45	100	17	10	7	34	5	7	24%	2.22	0.38	41%	6%	0.16	11%	16%
2016	22	83	6	6	0	18	0	0	18%	3.77	0.27	0%	0%	0.00	0%	0%
2017	46	120	9	4	5	41	1	3	11%	2.61	0.20	56%	4%	0.11	2%	7%
2018	59	79	7	1	6	54	4	4	8%	1.34	0.12	86%	7%	0.10	7%	7%
2019	48	65	9	9	0	47	0	0	2%	1.35	0.19	0%	0%	0.00	0%	0%
2020	53	62	3	2	1	50	1	1	6%	1.17	0.06	33%	2%	0.02	2%	2%
Overall	733	1632	1090	446	644	411	157	220	44%	2.23	1.49	59%	24%	0.88	21%	30%

Table 3. Main Results (Step 1)

For 733 NMEs approved by the FDA from 1998 to 2020, we observed that exaptation occurred in 220 NMEs, of which, in 157 NMEs, exaptation occurred more than adaptation. In addition, 322 NMEs had new usages after approval from the FDA, which accounts for 44% of all NMEs. On average, 2.23 usages were approved by the FDA as entry usages, followed by 1.49 emergent usages afterward per drug. Among them, we found that 0.88 emergent usage was from exaptation. Exaptation accounts for 59% in the emergence of usage, and even if all usages of NMEs are considered, that is, taken together with all original usages and all emergent usages, its impact accounts for 24% of the total.

The results show that the number of emergent usage decreases closer to the year 2020. This is because new usages were discovered sequentially based on clinical information gathered from the doctor or the pharmacist, not immediately after the approval of the NME. Hence, the number of emergent usages is proportional to the accumulated time since the approval of the NME. In this respect, the occurrence of exaptation can be understood as a part of the cumulative process that requires a certain amount of time.

Chapter 4.   Identifying the Origin of Exaptation and Capturing its Driving Force

4.1 Hypothesis

In chapter 2, we briefly discussed how spaces of the possible and open innovation can be reinterpreted with a focus on exaptation. Most previous studies on exaptation have focused on where the inventor's will cannot be involved in the emergence of technological innovation resulting from the ex-post view of exaptation in nature. Thereby, spaces of the possible have been somewhat viewed from a biased perspective. In this sense, exaptation still holds the fundamental limitation that its occurrence only depends on given luck, that is, serendipity. Focusing on this research gap, this study aims to present a balanced point of view on the occurrence of exaptation by separating two key elements that compose spaces of the possible.

4.1.1   Applicant-oriented Exaptation

4.1.1.1 Open Innovation

The pharmaceutical industry is a capital-intensive and technology-intensive industry; thus, it is regarded as one of the high-tech industries. Since the industry targets the human body, the whole process of drug development, clinical trials, and distribution to market bear astronomical expenses. For this reason, several pharmaceutical firms (Big pharma) developed innovative drugs and dominated the market based on the accumulated capital

and technology realizing economies of scale, which went on to constitute the basic industry structure in the past. As a result, the new entrants did not have enough capabilities to penetrate the market in terms of capital and technology. They relied on producing and selling generic copy drugs of the incumbents. However, with the advent of biosimilars, the pharmaceutical industry faced the transition of paradigm and opened a new era, that is, the era of open innovation. As biosimilars have come to open a new market, each of the pharmaceutical firms are striving to enhance their competitiveness in the market based on their internal capabilities, making full use of the external channels simultaneously. In other words, pharmaceutical firms of today are trying to secure their market competitiveness by integrating external resources and knowledge into internal capabilities, which will help them find the optimal point of exploitation and exploration (March, 1991). Celltrion and Samsung Biologics in Korea are the examples of success who have taken the advantage of open innovation. Both of them focused on Contract Manufacturing Organization (CMO) in the early stage to raise capital, through which they accumulated their capabilities to penetrate the market of biosimilars as the first-movers. In short, they succeeded to enhance their competitiveness in the market by focusing on the early strategy of open innovation.

As discussed in section 2.2, it is important to secure the diversity of combinations and linkages between the components of innovation, that is, technologies or products in order to increase the occurrence of exaptation. Firms, as entities of organizational behaviors, strive to survive in the market and secure continuous competitive advantages. In this

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sense, technological innovation is essential, and the R&D capabilities of a firm is directly related to its innovation performance since it is crucial in reorganizing the existing resources and knowledge to create new and advanced ones (Griliches, 1979; Rothaermel & Hess, 2007). Hence, firms use external channels to secure R&D capabilities via open innovation (Teece et al., 1997), which constitutes a way of M&A and strategic alliance in general. On the one hand, M&A refers to a management strategy in which two firms with independent structures are integrated into one governance structure (Hagedoorn & Duysters, 2002). It generally aims to help a firm secure the resources it does not have from the target firm. In other words, the primary motivation for a firm to promote M&A is to improve its innovation performance by securing R&D capabilities, as is from things such as human resources, technologies, and knowledge of the target firm (Hagedoorn and Duysters, 2002; Haspeslagh and Jameison, 1991; Puranam and Srikanth, 2007). On the other hand, strategic alliance refers to a management strategy that seeks to secure competitive advantages based on a mutual cooperation between firms (Eisenhardt & Schoonhoven, 1996), ensuring an independent governance structure. The primary motivation through which a firm expands its resources and knowledge pool is the learning of the affiliated firm (Dyer & Nobeoka, 2000; Kale et al., 2000; Khanna, Gulati & Nohria, 1998; Hamel, 1989).

Therefore, a firm that takes full advantage of either of the ways of open innovation can expand its resources and knowledge pool using external channels, and thus, can increase the diversity of combinations and linkages between them. In this sense, we can

infer that the possibility of the emergence of innovation can be increased in spaces of the possible, and the same for exaptation. Thus, we can formulate the hypothesis as follows.

H1a: A firm's open innovation strategy based on M&A and strategic alliances will have a positive effect on the occurrence of exaptation.

4.1.1.2 Portfolio diversification

As discussed in section 2.3, since the innovation performance of firms can lead to their profit maximization, they strive to secure the core resources and knowledge that are directly related to innovation performance. However, in a modern market with uncertainty, a firm cannot have all the resources and knowledge, which inevitably causes a problem of choosing as to which resources and knowledge to use. Consequently, a firm strives to minimize uncertainty under the given circumstances by maximizing the use of resources and knowledge, thereby attempting to achieve an optimal innovation performance. In this regard, a firm should carry the capabilities of sensing market changes, seizing new opportunities and transforming resources via reorganization. Teece et al. (1997) defined these capabilities as the dynamic capabilities of a firm, arguing that a firm could cope with uncertainty by concentrating the integration and reorganization of resources under the given circumstances. In other words, a firm can secure sustainable competitive advantages through capabilities that select appropriate resources and knowledge, and transform them under the changing market conditions (Eisenhardt & Martin, 2000).

Hence, a firm should manage its resources and knowledge effectively so as to ensure that it continuously survives in a dynamic market condition. From this point of view, dynamic capabilities can be said to be derived via the portfolio management of a firm's resources (Daniel, Ward & Franken, 2014; Killen, Hunt & Kleinschmidt, 2007; Sicotte, Drouin & Delerue, 2014).

The fact that a firm can integrate and reorganize the resources in various ways via the diverse resources held means that it is possible to form a diversified portfolio as well. In line with in section 4.1.1.1, this indicates that the diversity of combinations and linkages between the components in spaces of the possible can be increased. Thus, it is fair to state that the occurrence of exaptation can be increased by having a diverse portfolio.

H1b: A firm's drug class portfolio diversity will have a positive effect on the occurrence of exaptation.

4.1.2   Artifact-oriented Exaptation

4.1.2.1 Popularity

If a specific technology, knowledge, or product leads the trend in the industry paradigm, we can say that various sub- and related studies have been carried out in this regard. Expansion of a specific technology, knowledge, or product that belongs to the center of the industry paradigm could initiate various discussions of the concept itself, through which the quantitative accumulation process of the concept initiates the

qualitative expansion afterward. That is, specific technology, knowledge, or product acquires complexity encompassing various sub- and related concepts. In this sense, it can be understood as increasing the modularity of the element (Andriani & Carignani, 2014) via the improvement of near-decomposability (Simon, 1982). It is fair to state that the influence of specific technology, knowledge, or product within the industry paradigm can be substituted by the element's popularity; thus, the process of acquiring popularity within the industry paradigm can be equivalent to the process of increasing the modularity of components in spaces of the possible. Consequently, the occurrence of exaptation can be increased when a component by itself becomes popular enough to lead sub- and related debates.

H2a: The popularity of drug class to which a drug belongs will have a positive effect
on the occurrence of exaptation.

4.1.2.2 Initial versatility

If a specific element as itself inherently encompasses various sub- and related concepts, it can be said to have endogenous advantages in the emergence of innovation, regardless of the popularity it has within the industry paradigm. In other words, the given versatility of the element determines the possibility of the emergence of innovation, in that, it is interpreted as plausibly having an equivalent modularity as well. In this sense, it can be said that the element with high versatility favors the occurrence of exaptation from

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its innate modularity as a component itself in spaces of the possible.

H2b: The initial versatility of a drug will have a positive effect on the occurrence of

exaptation.

4.2 Empirical Setting

4.2.1 Variables

In line with the hypotheses stated in section 4.1, we gathered the manufacturer and drug information of 733 NMEs approved by the FDA from 1998 to 2020. Manufacturer-related information consists of the name of the manufacturer, financial information (total assets, revenues, the number of employees), information about the open innovation adoption[3], details about the number of NME pipelines owned, and information about the degree of drug class diversification in the NME pipelines. Drug-related information consists of information relating to the approval year of NME, dosage route, priority review[4], orphan review[5], the development frequency of drug class to which a drug belongs, indication and the number of original usages, and those of emergent usages.

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[3] As discussed in section 2.3, open innovation encompasses various sub concepts, in that, it refers to all the processes in which a firm integrates and utilizes its internal resources and capabilities with those on the outside to sustain its competitive advantage in the market. In this study, we compared the initial manufacturer at the time of drug approval and the present manufacturer for all NMEs. If the two were different, we further investigated the relationship between them, focusing on whether they went through M&A or the strategic alliance. If so, we assigned 1 as a dummy, 0 otherwise.

[4] It is a part of the review processes carried out by the FDA. Prior to drug approval, significant improvements in safety, effectiveness of the treatment, diagnosis, or prevention of diseases would be evaluated in comparison to the existing drugs with the same indication. If it shows significant improvements, it would be designated as a priority review to take actions on an application within 6 months. Otherwise, it would be designated as a standard review, thus, lagging in the priority of NME approval.

[5] It is a part of the review processes to confirm if a drug was developed for rare diseases.

Following this, we used manufacturer-related information as a proxy for applicant-oriented exaptation, and drug-related information as a proxy for artifact-oriented exaptation. Finally, we set four information areas as independent variables with regard to the hypotheses of sections 4.1.1 and 4.1.2. They are: open innovation adoption, the degree of drug class diversification in the NME pipelines, the popularity of drug class to which a drug belongs, and the number of original usages of a drug. Besides, we controlled some of the information that might directly or indirectly affect the occurrence of exaptation such as the financial information of a manufacturer (total assets & the number of employees), priority review, and orphan review adoption of a drug. The descriptive statistics are as follows (Table 4).

Variables	Description	Count	Mean	SD	Min.	Max.
Applicant Oriented						
TotalAsset	Average total assets of a firm for the specified period during 1998-2020 (unit: USD Billion)	733	990.625	5686.991	0.001	34921.930
Employees	Average employees of a firm for the specified period during 1998-2020 (unit: Thousand)	733	39.412	60.873	0.001	353.567
OpenInnov.	1 if the firm that has certain drug right has changed compared to the initial point of drug approval, 0 otherwise	733	0.308	0.462	0	1
Portfolio_Div.	Overall frequency of the firm's pipeline diversification regarding drug classes	733	10.074	8.545	0	26
Drug Oriented						
Review_S&P	1 if the drug has been designated as a fast-track for significant improvements in the safety, effectiveness, diagnosis, or prevention of serious conditions, 0 otherwise	733	0.516	0.500	0	1
Review_Orphan	1 if the drug that developed to treat rare medical conditions, thus, would not be profitable to produce without government assistance, 0 otherwise	733	0.356	0.479	0	1
DrugClass_Pop.	Overall frequency of the drug class that have been commercialized during 1998-2020	733	41.149	49.400	0	138
FDAuse_N.	Total number of the drug's FDA approved usage as a proxy of initial versatility	733	2.226	2.978	1	23
N		733				
Group		206				

Table 4. Overall Descriptive Statistics

4.2.2   Methodology

Generally, logistic regression is the most widely used method to analyze categorical and discrete variables as a non-linear model (Allison, 2012; Harrell, 2015; Long, 1997; Morrow-Howell & Proctor, 1993; Stokes, Davies & Koch, 2012). In this chapter, since we intend to examine hypotheses empirically by analyzing the correlations between the binary dependent variable and the four expected variables, it is appropriate to use logistic regression for the test. Hence, we used logistic regression to analyze the effects of four independent variables on the occurrence of exaptation and its degree based on the definitions of (3) and (4) provided in section 3.3.[6] In order to verify the robustness of the analysis, we further set the ratio variable "Tendency" and the continuous variable "No. of Exaptation" as the dependent variable and conducted linear regression respectively. We also conducted a mixed-effect linear regression to confirm the possibility of the influence that the manufacturers may have endogenously in the occurrence of exaptation (Appendix). Additionally, we tested the goodness of fit for the model by using the Hosmer-Lameshow test.

$$f_n(X) = \beta_0 + \beta_1 OpenInnov. + \beta_2 Portfolio\_Div. + \beta_3 DrugClass\_Pop. + \beta_4 FDAuse\_N. + Control + \varepsilon_i$$

$$(5)$$

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[6] Based on the continuous variable "Tendency", we reconstructed categorized discrete variables, that is, "Exapted Drug" with a positive tendency and "Exaptive Drug" with a tendency of more than 0.5 for indicating the emergence of exaptation and its continual occurrence thereafter, respectively.

4.2.3 Correlations

The overall correlations are as follows (Table 5). The number of employees of the manufacturer and the priority review adoption of a drug, which had been set as control variables, seemed to have multiple correlations with other variables. However, all the levels were acceptable. In all the variables, the maximum correlation value was 0.3888, which was less than 0.4. When the correlation has a value of more than 0.4, it is considered to have a moderate level of correlation in general (Akoglu, 2018).

Variables	TotalAssets	Employees	OpenInnov.	Portfolio_Div.	Review_S&P	Review_Orphan	DrugClass_Pop.	FDAuse_N.
TotalAssets	1.000							
Employees	-0.0393	1.000						
OpenInnov.	0.1244***	0.0040	1.000					
Portfolio_Div.	0.0436	0.3505***	0.1222***	1.000				
Review_S&P	-0.0216	0.0598	0.0027	0.0359	1.000			
Review_Orphan	0.0320	-0.0877**	-0.0153	-0.1756***	0.3843***	1.000		
DrugClass_Pop.	-0.0198	0.0888**	-0.0705	0.0163	0.2641***	0.3888***	1.000	
FDAuse_N.	-0.0458	0.1407***	-0.0578	0.1218***	0.1049***	-0.0365	0.0184	1.000

$^{*}\ p < 0.1,\ ^{**}\ p < 0.05,\ ^{***}\ p < 0.01$

Table 5. Overall Correlations

4.3 Results

As a non-linear regression model, the coefficient of logistic regression means a change in log odds as the corresponding variable increases. That is, the influence of the independent variable on the dependent variable cannot be assumed to have a linear relation. However, positive (+) or negative (-) represents the success probability that the value of the dependent variable changes from 0 to 1. Thus, each can be understood as an increase or decrease in the probability of success. In this regard, the success probability of this study surrogates the probability of occurrence of exaptation. If the value of a coefficient is positive (+), it means that an increase in the corresponding variable can increase the probability of the occurrence of exaptation. Conversely, if the value of a coefficient is negative (-), it means that an increase in the corresponding variable reduces the probability of the occurrence of exaptation. The main results of the logistic regression and additional linear regression model (OLS) for robustness tests are as follows (Table 6).

Variables	Exapted Drug		Exaptive Drug		Tendency	
	Logit				OLS	
	Coefficient	SE	Coefficient	SE	Coefficient	SE
Applicant-Oriented						
TotalAssets	1.12e-05	1.36e-05	2.02e-05	1.37e-05	3.08e-06	2.47e-06
Employees	0.0025*	0.0014	6.48e-05	0.0016	0.0003	0.0002
OpenInnov.	0.4968***	0.1767	0.6478***	0.1919	0.0930***	0.0306
Portfolio_Div.	0.1959*	0.1041	0.1730	0.1157	0.0339*	0.0179
Drug-Oriented						
Review_S&P	0.0205	0.1831	0.0722	0.2031	0.0101	0.0307
Review_Orphan	-0.2029	0.2083	0.0551	0.2298	-0.0131	0.0342
DrugClass_Pop.	-0.0412**	0.0196	-0.0663***	0.0232	-0.0080**	0.0031
FDAuse_N.	0.0840***	0.0319	0.0286	0.0278	0.0082*	0.0048
Constant	-1.3116***	0.1848	-1.6162***	0.2033	0.1679***	0.0297
Observations	733		733		733	
R-squared					0.0463	
Pseudo R-squared	0.0466		0.0407			

Standard errors in parentheses
* p<0.1, ** p<0.05, *** p<0.01

Table 6. Main results (Step 2)

4.3.1   Applicant-oriented Exaptation

For the 733 NMEs approved by the FDA from 1998 to 2020, at first, we observed that a firm's open innovation strategy has a positive effect on the occurrence of exaptation, as shown in Table 6. In this study, we examined the manufacturer's open innovation adoption focusing on the M&A and strategic alliance between firms, and as a result, statistically confirmed that open innovation can be used as a meaningful strategy for enhancing exaptation. This means that each firm can significantly increase the probability of the occurrence of exaptation in spaces of the possible as it can increase the diversity of combinations and linkages by expanding its resources and knowledge pool with open innovation. Second, we observed that a firm's drug class portfolio diversity has a positive effect on the occurrence of exaptation as well. By diversifying the pipelines in terms of drug class, a firm can secure continuous competitive advantages actively as it reorganizes its resources and knowledge in line with the changing market conditions. In other words, a firm can increase the diversity of the combinations and linkages of drug related resources and knowledge in spaces of the possible by diversifying its pipeline portfolio through various drug classes, and thus, can respond to the market uncertainty effectively. In this regard, the results confirm that a firm's portfolio diversification strategy can increase the possibility of discovering new usages by facilitating the combination and reorganization of its resources and knowledge related to drugs. This means that each firm can also increase the probability of the occurrence of exaptation via the diversification of its pipeline portfolio.

However, we found that only the open innovation strategy was observed to be significant in the continual occurrence of exaptation. That is, a firm's portfolio diversification strategy can significantly lead to the emergence of exaptation temporarily, but not continually. On the other hand, a firm's open innovation strategy is very useful not only for initiating exaptation, but also for continuing its occurrence thereafter. Based on the two main strategies mentioned above, we visualize the each applicant's frequency of exaptation as follows (Fig. 7).
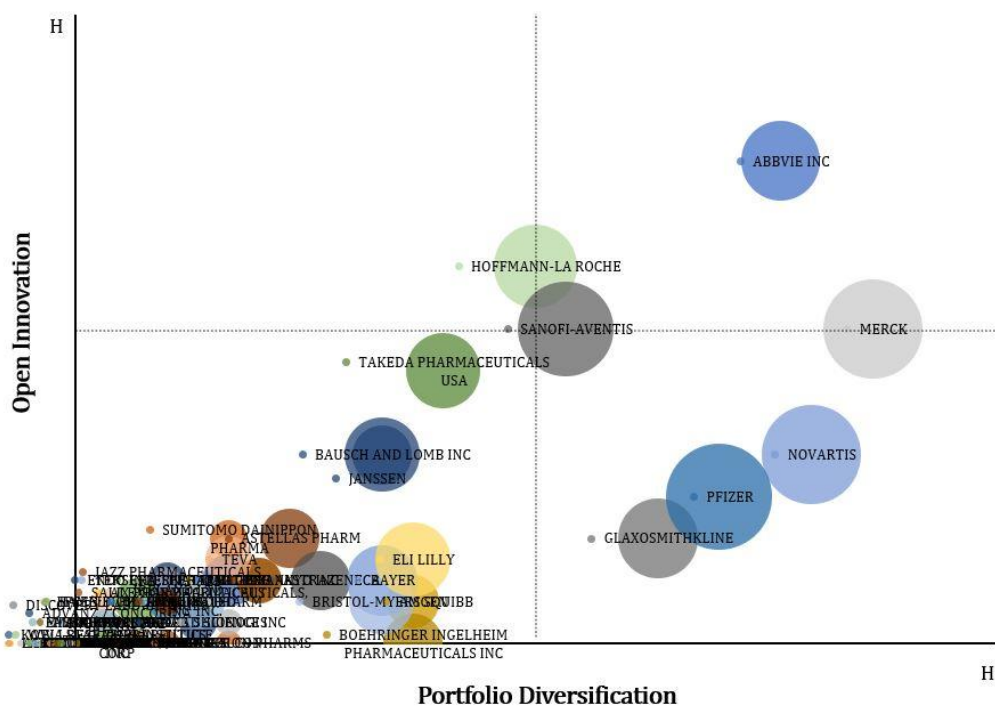
[7]**Figure 7.** Exaptation by Applicant

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[7] The size of the bubble indicates the frequency of exaptation.

As shown in Fig. 7, Firms in the 4th and 1st quadrants have the highest frequency of exaptation. We confirmed that their firm size in relation to the area of corporate finance such as total assets, revenues, and the number of employees were much larger than those of others. Specifically, ABBVIE was identified as the firm that exploits both the open innovation strategy and the portfolio diversification strategy in balance. Nevertheless, HOFFMANN-LA ROCHE, MERCK, NOVARTIS, PFIZER, and SANOFI-AVENTIS are ahead in the frequency of exaptation. The reason why ABBVIE, which does not reach their firm size, can show a similar level of exaptation frequency as those lies in the open innovation strategy. Therefore, it is worth stressing that the open innovation is the most effective strategy to enhance the occurrence of exaptation for a mid-sized firm with a certatin amount of financial power in particular.

4.3.2   Artifact-oriented Exaptation

Third, we observed that the development frequency of drug class to which a drug belongs, that is, the popularity of a drug class has a significant effect on both the initiation of exaptation and its continual occurrence. However, contrary to our expectations, it was found to have a negative effect, which means that, as the popularity of a drug class increases, the probability decreases not only in the case of emergence, but also in the continual occurrence of exaptation thereafter. This is because, presumably, the occurrence of adaptation precedes that of exaptation. For the drug class that already led the trend of the industry with high popularity, a newly approved NME would face fierce competition

for market penetration. In this regard, the drug development process is likely to focus on the characteristics that are different from the existing drugs, rather than the general characteristics of a drug class that can be used at a broad level. In other words, it may focus to bring unique characteristics within the part to which the original usage is most closely related, rather than being completely separated from the original usage. Hence, it is evident that, the higher the popularity of a drug class, the more likely it is for adaptation to occur prior to exaptation, and consequently, it is reasonable for it to have a negative effect on the emergence of exaptation as well as its occurrence afterward. For this reason, hypothesis H2a is rejected. Fourth, we observed that the number of original usages, that is, the versatility of the NME has a positive effect on the occurrence of exaptation. This means that, the greater the inherent versatility of the NME, the higher the probability of the occurrence of exaptation, just as having a high level of innate modularity in spaces of the possible. The result of OLS supports the robustness of logistic regression results and their interpretations in all the areas.
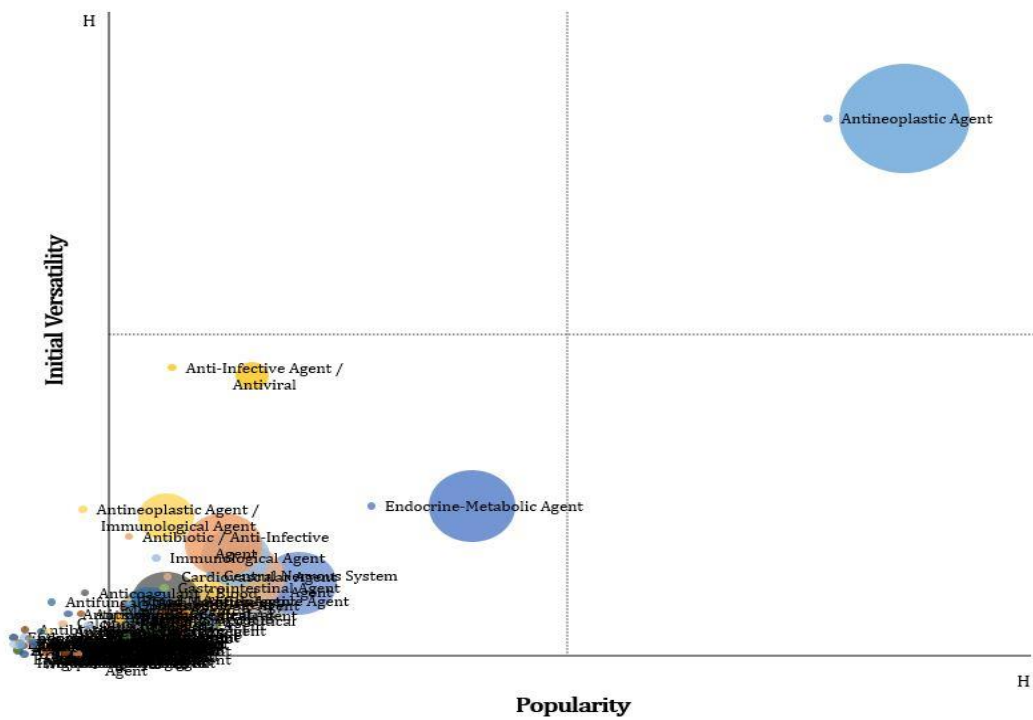
[8]**Figure 8.** Exaptation by Artifact (Drug Class)

Based on the main characteristics of section 4.3.2, we visualized the frequency of exaptation as above. As shown in Fig. 8, anti-neoplastic agents undoubtedly led the modern pharmaceutical industry as a trend. However, the frequency of exaptation is not directly proportional to the popularity of a drug class to which a drug belongs.

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[8] As in Fig. 7, the size of the bubble indicates the frequency of exaptation.

4.4 Robustness for Model

In this study, we examined the goodness of fit of the model using the Hosmer-Lameshow test to check if the constructed data is suitable for logistic regression. The null hypothesis of the Hosmer-Lameshow test is that the observed and expected proportions are the same across all estimations, that is, the specified model is correct. Hence, if the null hypothesis were not rejected, the data constructed can be understood as a suitable model for logistic regression. Just as the results shown in Table 7, the p-value was observed to be 0.3736 and 0.3913 for "Exapted Drug" and "Exaptive Drug," respectively, which means that the null hypothesis could not be rejected even in the significance level of 10 percent in both the cases. Therefore, the data constructed in this study can be said to be suitable as a model for logistic regression. The results of the Hosmer-Lameshow test are as follows (Table 7).

Goodness of fit for Logistic model	Exapted Drug	Exaptive Drug
Hosmer-Lemeshow test	$Number\ of\ Observation = 733$ $Number\ of\ Groups = 206$ $Hosmer - Lemeshow\ chi2(204) = 209.90$ $Prob > chi2 = 0.3736$	$Number\ of\ Observation = 733$ $Number\ of\ Groups = 206$ $Hosmer - Lemeshow\ chi2(204) = 208.95$ $Prob > chi2 = 0.3913$

H0: The observed and expected proportions are the same as across all estimations, that is, the fitted model is correct

Table 7. Hosmer-Lameshow Test for Logistic Regression (Goodness of Fit)

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Chapter 5.   Conclusions

5.1 Summary

In this study, we measured the frequency of exaptation for all the 733 NMEs approved by the FDA from 1998 to 2020. We set the variable "Tendency" to demonstrate the exaptation pattern of NMEs. In brief, we found that 1,632 original usages were approved as an entry usage of drugs and 1,090 usages were newly acquired thereafter. Of the 1,090 newly acquired usages, 644 of them were resulting from exaptation. Each NME had 2.23 original usages for approval, followed by 1.49 off-label usages afterward on average. From these acquired usages, we found that 0.88 usage was from exaptation. Taken together, we observed that the influence of exaptation on novelty generation was 59%. Considering all the usages of NMEs, it accounts for as much as 24%. In this sense, it is worth stressing that exaptation exerts a far greater influence on novelty generation than our expectations.

We identified a total of three factors that drive exaptation significantly. The fact that increasing the diversity of combinations and linkages between components in spaces of the possible constitutes a part where we can intentionally intervene with the teleology employing corporate strategies. Our results show that the open innovation strategy and portfolio diversification strategy of firms have a positive effect on the occurrence of exaptation. In particular, the open innovation strategy was found to be effective not only for the emergence of exaptation, but also for the continual occurrence of exaptation

afterward. Apart from the perspective of firms, the initial versatility of drugs itself was observed to be significant in the occurrence of exaptation. The popularity of a drug class was not found to be effectively inducing exaptation as the occurrence of adaptation precedes. In sum, all the hypotheses except H2a were confirmed to be statistically significant.

5.2 Implication

Previous studies have explored the unique characteristics of exaptation based on academic debates, thereby, have further on presented the implications of exaptation in the field of technological innovation. For this reason, although exaptation did come to the spotlight, it still suffered from the fundamental limitation that its occurrence solely relied on serendipity because of the absence of the identification of its driving forces. This study started with the objective of addressing this research gap and focused on the demonstration of exaptation. There are two steps that we followed: 1) measured the frequency of exaptation and 2) identified its fundamental driving forces. This study has expanded the concept of exaptation one step further in comparison to the previous studies, thereby proposing practical implications that are more suitable for the real world. In this respect, this study makes a meaningful contribution.

Our results show that exaptation can be driven by two different axes based on the firm (applicant) and the artifact. From this point of view, we can overcome the myth and the limitation of exaptation that its occurrence merely depends on the serendipity emerging

from the internal characteristics of the artifact itself. Most of all, this presents that we can facilitate the occurrence of exaptation structurally through corporate strategy.

5.2.1 Managerial Implication

Firms can foster exaptation using dual processes. First, they can take full advantage of open innovation at the inter-firm level. As discussed in section 4.3.1, it is the most effective strategy for facilitating the occurrence of exaptation. Each firm can expand its resources and knowledge pool through external channels in order to increase the diversity of combinations and linkages between them. In other words, a firm can structurally enhance its innovation performance; thus, it can survive and secure competitive advantages in the high-tech pharmaceutical industry.

Second, they can focus on the intra-firm level strategy by diversifying their pipeline portfolio. In this modern market with uncertainty, firms' dynamic capabilities are of paramount importance. Firms can maximize their innovation performance through the ability to select their resources and knowledge in line with the changing market conditions and transform their composition appropriately. In doing so, they can minimize the market's uncertainty. In this sense, pharmaceutical firms can integrate and reorganize information related to drugs by diversifying their pipeline portfolio into various drug classes. This is also consistent with the fact that a firm can structurally enhance its innovation performance through exaptation as aforementioned.

5.3 Limitation & Future Study

Despite these contributions, we present some limitations in the following. First, the reliability of databases and classification systems that were used to measure the frequency of exaptation. Although DrugDex and DrugBank are known as the most widely used commercial drug databases based on their reliability and accessibility, they still carry problems when gathering information about the emergent usages of drugs. For example, we found some cases where, although the information on off-label usages was listed in medical journals, it was omitted from databases. Further, we could not gather information relating to when each of the emergent usages were registered in the database. This indicates that a standard time to measure the frequency of exaptation has no options but just to be set as the present. In other words, it is impossible to trace back as to when the exaptation occurred for each of the emergent usages. Second, this study merely presents the academic relationship between technological innovation and exaptation by borrowing the concept of "spaces of the possible." As a proxy for technological innovation, we introduced innovation performance. Consequently, it is impossible to relate the figure information on the extent to which the exaptation pattern affects the actual innovation performance of a firm, and thus, the boundary on how much exaptation should be considered is still somewhat ambiguous.

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Appendix 1: ICD-10-CM Tabular List of Diseases and Injuries

ICD-10-CM TABULAR LIST of DISEASES and INJURIES

Table of Contents

Appendix Figure 1. ICD-10-CM Tabular List of Diseases and Injuries (General Classes)

Appendix 1: ICD-10-CM Tabular List of Diseases and Injuries

A00-A09	Intestinal infectious diseases
A15-A19	Tuberculosis
A20-A28	Certain zoonotic bacterial diseases
A30-A49	Other bacterial diseases
A50-A64	Infections with a predominantly sexual mode of transmission
A65-A69	Other spirochetal diseases
A70-A74	Other diseases caused by chlamydiae
A75-A79	Rickettsioses
A80-A89	Viral and prion infections of the central nervous system
A90-A99	Arthropod-borne viral fevers and viral hemorrhagic fevers
B00-B09	Viral infections characterized by skin and mucous membrane lesions
B10	Other human herpesviruses
B15-B19	Viral hepatitis
B20	Human immunodeficiency virus [HIV] disease
B25-B34	Other viral diseases
B35-B49	Mycoses
B50-B64	Protozoal diseases
B65-B83	Helminthiases
B85-B89	Pediculosis, acariasis and other infestations
B90-B94	Sequelae of infectious and parasitic diseases
B95-B97	Bacterial and viral infectious agents
B99	Other infectious diseases

Appendix Figure 2. ICD-10-CM (Subclass): Chapter 1

Appendix 1: ICD-10-CM Tabular List of Diseases and Injuries

C00-C14	Malignant neoplasms of lip, oral cavity and pharynx
C15-C26	Malignant neoplasms of digestive organs
C30-C39	Malignant neoplasms of respiratory and intrathoracic organs
C40-C41	Malignant neoplasms of bone and articular cartilage
C43-C44	Melanoma and other malignant neoplasms of skin
C45-C49	Malignant neoplasms of mesothelial and soft tissue
C50	Malignant neoplasms of breast
C51-C58	Malignant neoplasms of female genital organs
C60-C63	Malignant neoplasms of male genital organs
C64-C68	Malignant neoplasms of urinary tract
C69-C72	Malignant neoplasms of eye, brain and other parts of central nervous system
C73-C75	Malignant neoplasms of thyroid and other endocrine glands
C7A	Malignant neuroendocrine tumors
C7B	Secondary neuroendocrine tumors
C76-C80	Malignant neoplasms of ill-defined, other secondary and unspecified sites
C81-C96	Malignant neoplasms of lymphoid, hematopoietic and related tissue
D00-D09	In situ neoplasms
D10-D36	Benign neoplasms, except benign neuroendocrine tumors
D3A	Benign neuroendocrine tumors
D37-D48	Neoplasms of uncertain behavior, polycythemia vera and myelodysplastic syndromes
D49	Neoplasms of unspecified behavior

Appendix Figure 3. ICD-10-CM (Subclass): Chapter 2

Appendix 1: ICD-10-CM Tabular List of Diseases and Injuries

D50-D53	Nutritional anemias
D55-D59	Hemolytic anemias
D60-D64	Aplastic and other anemias and other bone marrow failure syndromes
D65-D69	Coagulation defects, purpura and other hemorrhagic conditions
D70-D77	Other disorders of blood and blood-forming organs
D78	Intraoperative and postprocedural complications of the spleen
D80-D89	Certain disorders involving the immune mechanism

Appendix Figure 4. ICD-10-CM (Sub class): Chapter 3

E00-E07	Disorders of thyroid gland
E08-E13	Diabetes mellitus
E15-E16	Other disorders of glucose regulation and pancreatic internal secretion
E20-E35	Disorders of other endocrine glands
E36	Intraoperative complications of endocrine system
E40-E46	Malnutrition
E50-E64	Other nutritional deficiencies
E65-E68	Overweight, obesity and other hyperalimentation
E70-E88	Metabolic disorders
E89	Postprocedural endocrine and metabolic complications and disorders, not elsewhere classified

Appendix Figure 5. ICD-10-CM (Subclass): Chapter 4

Appendix 1: ICD-10-CM Tabular List of Diseases and Injuries

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F01-F09    Mental disorders due to known physiological conditions
F10-F19    Mental and behavioral disorders due to psychoactive substance use
F20-F29    Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders
F30-F39    Mood [affective] disorders
F40-F48    Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders
F50-F59    Behavioral syndromes associated with physiological disturbances and physical factors
F60-F69    Disorders of adult personality and behavior
F70-F79    Intellectual disabilities
F80-F89    Pervasive and specific developmental disorders
F90-F98    Behavioral and emotional disorders with onset usually occurring in childhood and adolescence
F99        Unspecified mental disorder
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Appendix Figure 6. ICD-10-CM (Sub class): Chapter 5

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G00-G09    Inflammatory diseases of the central nervous system
G10-G14    Systemic atrophies primarily affecting the central nervous system
G20-G26    Extrapyramidal and movement disorders
G30-G32    Other degenerative diseases of the nervous system
G35-G37    Demyelinating diseases of the central nervous system
G40-G47    Episodic and paroxysmal disorders
G50-G59    Nerve, nerve root and plexus disorders
G60-G65    Polyneuropathies and other disorders of the peripheral nervous system
G70-G73    Diseases of myoneural junction and muscle
G80-G83    Cerebral palsy and other paralytic syndromes
G89-G99    Other disorders of the nervous system
```

Appendix Figure 7. ICD-10-CM (Subclass): Chapter 6

Appendix 1: ICD-10-CM Tabular List of Diseases and Injuries

H00-H05	Disorders of eyelid, lacrimal system and orbit
H10-H11	Disorders of conjunctiva
H15-H22	Disorders of sclera, cornea, iris and ciliary body
H25-H28	Disorders of lens
H30-H36	Disorders of choroid and retina
H40-H42	Glaucoma
H43-H44	Disorders of vitreous body and globe
H46-H47	Disorders of optic nerve and visual pathways
H49-H52	Disorders of ocular muscles, binocular movement, accommodation and refraction
H53-H54	Visual disturbances and blindness
H55-H57	Other disorders of eye and adnexa
H59	Intraoperative and postprocedural complications and disorders of eye and adnexa, not elsewhere classified

Appendix Figure 8. ICD-10-CM (Subclass): Chapter 7

H60-H62	Diseases of external ear
H65-H75	Diseases of middle ear and mastoid
H80-H83	Diseases of inner ear
H90-H94	Other disorders of ear
H95	Intraoperative and postprocedural complications and disorders of ear and mastoid process, not elsewhere classified

Appendix Figure 9. ICD-10-CM (Subclass): Chapter 8

Appendix 1: ICD-10-CM Tabular List of Diseases and Injuries

I00-I02	Acute rheumatic fever
I05-I09	Chronic rheumatic heart diseases
I10-I16	Hypertensive diseases
I20-I25	Ischemic heart diseases
I26-I28	Pulmonary heart disease and diseases of pulmonary circulation
I30-I52	Other forms of heart disease
I60-I69	Cerebrovascular diseases
I70-I79	Diseases of arteries, arterioles and capillaries
I80-I89	Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified
I95-I99	Other and unspecified disorders of the circulatory system

Appendix Figure 10. ICD-10-CM (Subclass): Chapter 9

J00-J06	Acute upper respiratory infections
J09-J18	Influenza and pneumonia
J20-J22	Other acute lower respiratory infections
J30-J39	Other diseases of upper respiratory tract
J40-J47	Chronic lower respiratory diseases
J60-J70	Lung diseases due to external agents
J80-J84	Other respiratory diseases principally affecting the interstitium
J85-J86	Suppurative and necrotic conditions of the lower respiratory tract
J90-J94	Other diseases of the pleura
J95	Intraoperative and postprocedural complications and disorders of respiratory system, not elsewhere classified
J96-J99	Other diseases of the respiratory system

Appendix Figure 11. ICD-10-CM (Subclass): Chapter 10

Appendix 1: ICD-10-CM Tabular List of Diseases and Injuries

K00-K14   Diseases of oral cavity and salivary glands
K20-K31   Diseases of esophagus, stomach and duodenum
K35-K38   Diseases of appendix
K40-K46   Hernia
K50-K52   Noninfective enteritis and colitis
K55-K64   Other diseases of intestines
K65-K68   Diseases of peritoneum and retroperitoneum
K70-K77   Diseases of liver
K80-K87   Disorders of gallbladder, biliary tract and pancreas
K90-K95   Other diseases of the digestive system

Appendix Figure 12. ICD-10-CM (Subclass): Chapter 11

L00-L08   Infections of the skin and subcutaneous tissue
L10-L14   Bullous disorders
L20-L30   Dermatitis and eczema
L40-L45   Papulosquamous disorders
L49-L54   Urticaria and erythema
L55-L59   Radiation-related disorders of the skin and subcutaneous tissue
L60-L75   Disorders of skin appendages
L76   Intraoperative and postprocedural complications of skin and subcutaneous tissue
L80-L99   Other disorders of the skin and subcutaneous tissue

Appendix Figure 13. ICD-10-CM (Subclass): Chapter 12

Appendix 1: ICD-10-CM Tabular List of Diseases and Injuries

M00-M02	Infectious arthropathies
M04	Autoinflammatory syndromes
M05-M14	Inflammatory polyarthropathies
M15-M19	Osteoarthritis
M20-M25	Other joint disorders
M26-M27	Dentofacial anomalies [including malocclusion] and other disorders of jaw
M30-M36	Systemic connective tissue disorders
M40-M43	Deforming dorsopathies
M45-M49	Spondylopathies
M50-M54	Other dorsopathies
M60-M63	Disorders of muscles
M65-M67	Disorders of synovium and tendon
M70-M79	Other soft tissue disorders
M80-M85	Disorders of bone density and structure
M86-M90	Other osteopathies
M91-M94	Chondropathies
M95	Other disorders of the musculoskeletal system and connective tissue
M96	Intraoperative and postprocedural complications and disorders of musculoskeletal system, not elsewhere classified
M97	Periprosthetic fracture around internal prosthetic joint
M99	Biomechanical lesions, not elsewhere classified

Appendix Figure 14. ICD-10-CM (Subclass): Chapter 13

Appendix 1: ICD-10-CM Tabular List of Diseases and Injuries

N00-N08	Glomerular diseases
N10-N16	Renal tubulo-interstitial diseases
N17-N19	Acute kidney failure and chronic kidney disease
N20-N23	Urolithiasis
N25-N29	Other disorders of kidney and ureter
N30-N39	Other diseases of the urinary system
N40-N53	Diseases of male genital organs
N60-N65	Disorders of breast
N70-N77	Inflammatory diseases of female pelvic organs
N80-N98	Noninflammatory disorders of female genital tract
N99 classified	Intraoperative and postprocedural complications and disorders of genitourinary system, not elsewhere

Appendix Figure 15. ICD-10-CM (Subclass): Chapter 14

O00-O08	Pregnancy with abortive outcome
O09	Supervision of high risk pregnancy
O10-O16	Edema, proteinuria and hypertensive disorders in pregnancy, childbirth and the puerperium
O20-O29	Other maternal disorders predominantly related to pregnancy
O30-O48	Maternal care related to the fetus and amniotic cavity and possible delivery problems
O60-O77	Complications of labor and delivery
O80-O82	Encounter for delivery
O85-O92	Complications predominantly related to the puerperium
O94-O9A	Other obstetric conditions, not elsewhere classified

Appendix Figure 16. ICD-10-CM (Subclass): Chapter 15

Appendix 1: ICD-10-CM Tabular List of Diseases and Injuries

P00-P04   Newborn affected by maternal factors and by complications of pregnancy, labor, and delivery
P05-P08   Disorders of newborn related to length of gestation and fetal growth
P09   Abnormal findings on neonatal screening
P10-P15   Birth trauma
P19-P29   Respiratory and cardiovascular disorders specific to the perinatal period
P35-P39   Infections specific to the perinatal period
P50-P61   Hemorrhagic and hematological disorders of newborn
P70-P74   Transitory endocrine and metabolic disorders specific to newborn
P76-P78   Digestive system disorders of newborn
P80-P83   Conditions involving the integument and temperature regulation of newborn
P84   Other problems with newborn
P90-P96   Other disorders originating in the perinatal period

Appendix Figure 17. ICD-10-CM (Subclass): Chapter 16

Q00-Q07   Congenital malformations of the nervous system
Q10-Q18   Congenital malformations of eye, ear, face and neck
Q20-Q28   Congenital malformations of the circulatory system
Q30-Q34   Congenital malformations of the respiratory system
Q35-Q37   Cleft lip and cleft palate
Q38-Q45   Other congenital malformations of the digestive system
Q50-Q56   Congenital malformations of genital organs
Q60-Q64   Congenital malformations of the urinary system
Q65-Q79   Congenital malformations and deformations of the musculoskeletal system
Q80-Q89   Other congenital malformations
Q90-Q99   Chromosomal abnormalities, not elsewhere classified

Appendix Figure 18. ICD-10-CM (Subclass): Chapter 17

Appendix 1: ICD-10-CM Tabular List of Diseases and Injuries

R00-R09	Symptoms and signs involving the circulatory and respiratory systems
R10-R19	Symptoms and signs involving the digestive system and abdomen
R20-R23	Symptoms and signs involving the skin and subcutaneous tissue
R25-R29	Symptoms and signs involving the nervous and musculoskeletal systems
R30-R39	Symptoms and signs involving the genitourinary system
R40-R46	Symptoms and signs involving cognition, perception, emotional state and behavior
R47-R49	Symptoms and signs involving speech and voice
R50-R69	General symptoms and signs
R70-R79	Abnormal findings on examination of blood, without diagnosis
R80-R82	Abnormal findings on examination of urine, without diagnosis
R83-R89	Abnormal findings on examination of other body fluids, substances and tissues, without diagnosis
R90-R94	Abnormal findings on diagnostic imaging and in function studies, without diagnosis
R97	Abnormal tumor markers
R99	Ill-defined and unknown cause of mortality

Appendix Figure 19. ICD-10-CM (Subclass): Chapter 18

Appendix 1: ICD-10-CM Tabular List of Diseases and Injuries

S00-S09	Injuries to the head
S10-S19	Injuries to the neck
S20-S29	Injuries to the thorax
S30-S39	Injuries to the abdomen, lower back, lumbar spine, pelvis and external genitals
S40-S49	Injuries to the shoulder and upper arm
S50-S59	Injuries to the elbow and forearm
S60-S69	Injuries to the wrist, hand and fingers
S70-S79	Injuries to the hip and thigh
S80-S89	Injuries to the knee and lower leg
S90-S99	Injuries to the ankle and foot
T07	Injuries involving multiple body regions
T14	Injury of unspecified body region
T15-T19	Effects of foreign body entering through natural orifice
T20-T25	Burns and corrosions of external body surface, specified by site
T26-T28	Burns and corrosions confined to eye and internal organs
T30-T32	Burns and corrosions of multiple and unspecified body regions
T33-T34	Frostbite
T36-T50	Poisoning by, adverse effect of and underdosing of drugs, medicaments and biological substances
T51-T65	Toxic effects of substances chiefly nonmedicinal as to source
T66-T78	Other and unspecified effects of external causes
T79	Certain early complications of trauma
T80-T88	Complications of surgical and medical care, not elsewhere classified

Appendix Figure 20. ICD-10-CM (Subclass): Chapter 19

Appendix 1: ICD-10-CM Tabular List of Diseases and Injuries

V00-X58	Accidents
V00-V99	Transport accidents
V00-V09	Pedestrian injured in transport accident
V10-V19	Pedal cycle rider injured in transport accident
V20-V29	Motorcycle rider injured in transport accident
V30-V39	Occupant of three-wheeled motor vehicle injured in transport accident
V40-V49	Car occupant injured in transport accident
V50-V59	Occupant of pick-up truck or van injured in transport accident
V60-V69	Occupant of heavy transport vehicle injured in transport accident
V70-V79	Bus occupant injured in transport accident
V80-V89	Other land transport accidents
V90-V94	Water transport accidents
V95-V97	Air and space transport accidents
V98-V99	Other and unspecified transport accidents
W00-X58	Other external causes of accidental injury
W00-W19	Slipping, tripping, stumbling and falls
W20-W49	Exposure to inanimate mechanical forces
W50-W64	Exposure to animate mechanical forces
W65-W74	Accidental non-transport drowning and submersion
W85-W99	Exposure to electric current, radiation and extreme ambient air temperature and pressure
X00-X08	Exposure to smoke, fire and flames
X10-X19	Contact with heat and hot substances
X30-X39	Exposure to forces of nature
X50	Overexertion and strenuous or repetitive movements
X52-X58	Accidental exposure to other specified factors
X71-X83	Intentional self-harm
X92-Y09	Assault
Y21-Y33	Event of undetermined intent
Y35-Y38	Legal intervention, operations of war, military operations, and terrorism
Y62-Y84	Complications of medical and surgical care
Y62-Y69	Misadventures to patients during surgical and medical care
Y70-Y82	Medical devices associated with adverse incidents in diagnostic and therapeutic use
Y83-Y84	Surgical and other medical procedures as the cause of abnormal reaction of the patient, or of later complication, without mention of misadventure at the time of the procedure
Y90-Y99	Supplementary factors related to causes of morbidity classified elsewhere

Appendix Figure 21. ICD-10-CM (Subclass): Chapter 20

Appendix 1: ICD-10-CM Tabular List of Diseases and Injuries

Z00-Z13   Persons encountering health services for examinations
Z14-Z15   Genetic carrier and genetic susceptibility to disease
Z16   Resistance to antimicrobial drugs
Z17   Estrogen receptor status
Z18   Retained foreign body fragments
Z19   Hormone sensitivity malignancy status
Z20-Z29   Persons with potential health hazards related to communicable diseases
Z30-Z39   Persons encountering health services in circumstances related to reproduction
Z40-Z53   Encounters for other specific health care
Z55-Z65   Persons with potential health hazards related to socioeconomic and psychosocial circumstances
Z66   Do not resuscitate status
Z67   Blood type
Z68   Body mass index (BMI)
Z69-Z76   Persons encountering health services in other circumstances
Z77-Z99   Persons with potential health hazards related to family and personal history and certain conditions influencing health status

Appendix Figure 22. ICD-10-CM (Subclass): Chapter 21

U00-U49   Provisional assignment of new diseases of uncertain etiology or emergency use

Appendix Figure 23. ICD-10-CM (Subclass): Chapter 22

Appendix 2: Robustness

Exapted Drug	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)
Applicant-Oriented						
TotalAssets	1.16e-05 (1.35e-05)	1.46e-05 (1.34e-05)	1.03e-05 (1.35e-05)	1.58e-05 (1.34e-05)	1.81e-05 (1.34e-05)	1.74e-05 (1.35e-05)
Employees	0.0035*** (0.0013)	0.0025* (0.0013)	0.0027** (0.0014)	0.0038*** (0.0013)	0.0030** (0.0013)	0.0033** (0.0013)
OpenInnov_M&A.	0.5246*** (0.1730)		0.4832*** (0.1746)			
Portfolio_Div.		0.2376** (0.1011)	0.2051** (0.1027)			
Drug-Oriented						
Review_S&P	0.0638 (0.1777)	0.0369 (0.1780)	0.0332 (0.1788)	0.1259 (0.1789)	0.0106 (0.1789)	0.0639 (0.1810)
Review_Orphan	-0.4454** (0.1916)	-0.3752* (0.1938)	-0.3778* (0.1948)	-0.3053 (0.2013)	-0.4188** (0.1920)	-0.2710 (0.2029)
DrugClass_Pop.				-0.0430** (0.0194)		-0.0433** (0.0195)
FDAuse_N.					0.0803*** (0.0310)	0.0813** (0.0316)
Constant	-1.0621*** (0.1444)	-1.1106*** (0.1631)	-1.2368*** (0.1714)	-0.8168*** (0.1354)	-1.0382*** (0.1431)	-0.9626*** (0.1473)
Observations	733	733	733	733	733	733
R-squared						
Pseudo R-squared	0.0275	0.0235	0.0319	0.0231	0.0265	0.0322

Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Appendix Table 1. Robustness (Exapted Drug)

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Appendix 2: Robustness

Exaptive Drug	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)
Applicant-Oriented						
TotalAssets	2.13e-05 (1.36e-05)	2.60e-05* (1.34e-05)	2.02e-05 (1.36e-05)	2.69e-05** (1.35e-05)	2.83e-05** (1.34e-05)	2.74e-05** (1.35e-05)
Employees	0.0005 (0.0015)	-0.0005 (0.0016)	0.0003 (0.0016)	0.0010 (0.0015)	0.0003 (0.0015)	0.0009 (0.0015)
OpenInnov_M&A.	0.7027*** (0.1880)		0.6691*** (0.1895)			
Portfolio_Div.		0.2143 (0.1124)	0.1688 (0.1151)			
Drug-Oriented						
Review_S&P	0.0529 (0.1981)	0.0304 (0.1977)	0.0271 (0.1992)	0.1367 (0.1988)	0.0419 (0.1982)	0.1155 (0.2005)
Review_Orphan	-0.2390 (0.2116)	-0.1774 (0.2134)	-0.1813 (0.2155)	-0.0230 (0.2222)	-0.2349 (0.2102)	-0.0105 (0.2226)
DrugClass_Pop.				-0.0693*** (0.0231)		-0.0693*** (0.0231)
FDAuse_N.					0.0252 (0.0275)	0.0248 (0.0273)
Constant	-1.5381*** (0.1644)	-1.4927*** (0.1814)	-1.6783*** (0.1931)	-1.1810*** (0.1513)	-1.3458*** (0.1547)	-1.2259*** (0.1594)
Observations	733	733	733	733	733	733
R-squared						
Pseudo R-squared	0.0250	0.0117	0.0278	0.0200	0.0265	0.0210

Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Appendix Table 2. Robustness (Exaptive Drug)

Appendix 2: Robustness

Tendency	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)
Applicant-Oriented						
TotalAssets	3.32e-06 (2.48e-06)	3.98e-06 (2.48e-06)	3.07e-06 (2.48e-06)	4.20e-06* (2.47e-06)	4.52e-06* (2.48e-06)	4.35e-06* (2.47e-06)
Employees	0.0004* (0.0002)	0.0002 (0.0002)	0.0003 (0.0002)	0.0005** (0.0002)	0.0004 (0.0002)	0.0004* (0.0002)
OpenInnov_M&A.	0.1024*** (0.0305)		0.0954*** (0.0306)			
Portfolio_Div.		0.0406** (0.0179)	0.0339* (0.0179)			
Drug-Oriented						
Review_S&P	0.0116 (0.0304)	0.0069 (0.0307)	0.0066 (0.0305)	0.0229 (0.0307)	0.0070 (0.0308)	0.0170 (0.0309)
Review_Orphan	-0.0565* (0.0318)	-0.0457 (0.0325)	-0.0457 (0.0323)	-0.0285 (0.0339)	-0.0553* (0.0321)	-0.0249 (0.0339)
DrugClass_Pop.				-0.0084*** (0.0031)		-0.0084*** (0.0031)
FDAuse_N.					0.0080* (0.0048)	0.0080* (0.0048)
Constant	0.1938*** (0.0245)	0.1897*** (0.0274)	0.1670*** (0.0282)	0.2399*** (0.0235)	0.2100*** (0.0244)	0.2256*** (0.0250)
Observations	733	733	733	733	733	733
R-squared	0.0288	0.0207	0.0336	0.0233	0.0175	0.0271
Pseudo R-squared						

Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Appendix Table 3. Robustness (Tendency)

Appendix 2: Robustness (Mixed-Effects Regression Model)

Variables	Exapted Drug		Exaptive Drug		Tendency	
	Mixed-Effects Logit				Mixed-Effects ML	
	Coefficient	SE	Coefficient	SE	Coefficient	SE
Applicant-Oriented						
TotalAssets	1.12e-05	1.36e-05	2.02e-05	1.37e-05	3.08e-06	2.45e-06
Employees	0.0025*	0.0014	6.48e-05	0.0016	0.0003	0.0002
OpenInnov.	0.4968***	0.1767	0.6478***	0.1919	0.0930***	0.0305
Portfolio_Div.	0.1959*	0.1041	0.0173	0.0116	0.0339*	0.1775
Drug-Oriented						
Review_S&P	0.0205	0.1831	0.0722	0.2031	0.0101	0.0305
Review_Orphan	-0.2029	0.2083	0.0551	0.2298	-0.0130	0.0340
DrugClass_Pop.	-0.0412**	0.0196	-0.0663***	0.0232	-0.0080**	0.0031
FDAUse_N.	0.0840***	0.0319	0.0286	0.0278	0.0082*	0.0047
Constant	-1.3116***	0.1848	-1.6162***	0.2033	0.1679***	0.0296
Observations	733		733		733	
Number of groups	206		206		206	

Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Appendix Table 4. Robustness (Mixed-Effects Regression Model)

Appendix 2: Robustness (No. of Exaptation)

Variables	No. of Exaptation		No. of Exaptation	
	OLS		Mixed-Effects ML	
	Coefficient	SE	Coefficient	SE
Applicant-Oriented				
TotalAssets	-1.05e-06	1.41e-05	-1.07e-06	1.44e-05
Employees	0.0004	0.0014	0.0003	0.0014
OpenInnov.	0.6500***	0.1745	0.6553***	0.1742
Portfolio_Div.	0.0434	0.1017	0.0450	0.1053
Drug-Oriented				
Review_S&P	0.1949	0.1751	0.1983	0.1740
Review_Orphan	-0.0435	0.1017	-0.0465	0.1937
DrugClass_Pop.	-0.0346*	0.0177	-0.0356**	0.0176
FDAuse_N.	0.0819***	0.0271	0.0828***	0.0270
Constant	0.4959***	0.1694	0.4941***	0.1690
Observations	733		733	
R-squared	0.0409			
Pseudo R-squared				

Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Appendix Table 5. Robustness (No. of Exaptation)

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Abstract (Korean)

기존의 것과는 전혀 다른 용도 및 기능으로 진화된 형질이 현재의 영역에서 활용되는 일련의 패턴을 뜻하는 굴절적응 (Exaptation)은 새로움의 창발 (Novelty generation)로 말미암아 혁신을 견인하는 핵심원리임에도 불구하고 여지껏 그에 상응하는 충분한 연구가 부재한 실정이다. 비록 몇 가지 선행연구를 통해 굴절적응의 역할과 함의에 대한 면밀한 조사 및 분석이 이루어졌지만, 대부분의 경우 현상의 실증보다는 개념이 갖는 학술적 논의에 오롯이 그 초점을 집중한다는 점에서 분명한 한계를 보여주고 있다. 더불어 해당 현상이 갖는 사후성에 입각하여 다소 편향된 시각에서 굴절적응의 발생을 단순히 우연한 기회 (Serendipity)로 말미암아 외생적으로 주어지는 것으로 바라보았다.

따라서 본 연구에서는 기존의 편향된 통념과 한계점에서 벗어나 보다 균형 잡힌 시각에서 굴절적응을 재조명하고자 한다. 이에 제약산업을 활용하여 굴절적응의 빈도를 측정하고 그 동인을 정량적으로 분석함으로써, 현실세계에서 혁신 창발의 핵심원리로서 굴절적응이 갖는 영향력을 실증하였다. 더불어 가능성의 공간 (Spaces of the possible)을 이루는 두 가지 핵심요소에 주목하여 굴절적응의 동인을 기업과 인공물로 각각 이분화함으로써 그 발생을 구조적으로 견인할 수 있는 현실적인 대안을 제시하였다.

분석 결과 FDA 승인 이후 신약이 획득한 새로운 용도 (Off-label usage) 중 약 59%가 굴절적응으로부터 기인한 것으로 나타났고, 전체 신약의 30%에서

굴절적응이 발생한 것을 확인하였다. 덧붙여 기업의 개방형 혁신 전략과 포트폴리오 다각화 전략을 통해 굴절적응의 발생을 구조적으로 유도할 수 있음을 확인하였다.