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O Impacto da Biotecnologia sobre as Novas Entidades Químicas

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Resumo:

Este artigo parte da seguinte questão: as biotecnologias têm um impacto positivo sobre a eficácia da P&D? Para respondê-la, elaboramos duas hipóteses baseadas na literatura: (H1) As tecnologias farmacêuticas tiveram um efeito positivo sobre os resultados tecnológicos no curto prazo; (H2) As biotecnologias têm um efeito positivo sobre os resultados tecnológicos a longo prazo. Desenvolvemos um modelo VEC para medir o impacto das patentes farmacêuticas e da biotecnologia a curto e longo prazo. Nossos cálculos nos permitiram confirmar H2. No entanto, no curto prazo, identificamos a NCE passada como a única variável significativa para a NCE futura. Nosso artigo contribui trazendo uma análise de séries temporais para a economia da inovação e respondendo a outro assunto relevante entre a economia do conhecimento e da inovação que é o acréscimo de conhecimento útil feito por patentes.

Palavras-chave: Biotecnologia; Indústria farmacêutica; Propriedade Intelectual; Inovação.

JEL: O3; O31; O32; O34.

Área Temática: 5.6 - Inovação, competências e competitividade.

The Impact of Biotechnologies on New Chemical Entities (NCE)

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Abstract: This article departs from the following question: does biotechnologies have a positive impact over R&D effectiveness? In order to answer it we elaborate two hypotheses based on the literature: (H1) Pharmaceutical technologies had a positive effect on technological outputs at the short run; (H2) Biotechnologies have a positive effect on technological outputs at the long run. We conducted a VEC model to measure the impact of pharma and biotech patents in the short and long run. Our calculations allowed us to confirm H2. Nevertheless, in the short run we identify the Past NCE as the only significant variable to future NCE. Our article contributes by bringing a time series analyses to the economics of innovation and by answering another relevant subject among the economics of knowledge and innovation that is the additions in useful knowledge made by patents.

Keywords: Biotechnology; Pharmaceutical Industry; Intellectual Property; Innovation.

JEL: O3, O31, O32, O34.

Introduction

The pharmaceutical industry is a recurrent theme among studies on the field of economics. For a while some scholars focus their attention at the productivity crises in the industry' R&D. That fact consists of a non-apparent and proportional correlation between the New Molecular Entities (NME) - or New Chemical entities (NCE)-, approved by the FDA, and the R&D expenditures and patent applications. In other words, the industry is expending more on research activities and producing, relatively, much less, innovations.

Part of the literature that deals with R&D crises is highly focused on cost perspective analyses, this approach left important technological aspects aside (Comanor; Scherer, 2013; DiMasi 2000; Grabowski; Vernon, 2000; Grabowski; Vernon, 1994). Nevertheless, costs are too simplistic in order to understand technological evolution.

The literature focused on technical change (Hopkins et al. 2007;Martin, Nightingale, and Kraft 2008, Nightingale 2000; Nightingale and Martin 2004; Nightingale and Madhi, 2006; among others) shows that the industry evolves towards a marked division of innovative labor and specialization of research activities (Gambardela, 1995; Hopkins, Nightingale and Baden-Fuller 2012; Matos, 2016; Schweizer, 2005). As result, there is a risk reduction and a greater ability to acquire new technological skills, that, in some cases, can completely replace elements among the innovative process (Cassiman and Veuglers, 2006; Hagedoorn *et al.,* 2012 and Hess and Roathermel, 2011).

Both cost perspective and the technological evolution approach carry with them an interesting conclusion: the large pharmaceutical companies have tried to incorporate biotechnology in order to increase their R&D effectiveness.

In this article we made a simple but extremely relevant question: Does biotechnologies have a positive impact over R&D effectiveness? If so, this impact is greater over the years. In order to answer this question, this article builds a VECM model that will shed light on the impact of biotechnologies on NCEs.

This article is divided into three sections. The first one discusses the evolution of technology in the drug discovery activities. Based on that we derived our hypothesis. The second section explains the methodology. The third section discuss the model results and, finally, we present the conclusion.

1 Drug discovery main Technologies evolution: before and after the biotechnologies.

This section aims at discussing the technological evolution of drug discovery techniques. Here we show two trajectories one based on the core pharmaceutical competences and the other based on biotechnology competences. Due to these trajectories' differences in techniques and period of time, we can establish our two hypotheses.

1.1 R&D techniques within the pharmaceutical related competences.

This article builds its hypotheses having the research based pharmaceutical industry as study object. At its beginning (before 1930) the pharmaceutical enterprises were not research dedicated or they did not have a science-based method of research, this process was consolidated in the 1930s.

At that time, based on chemistry competences the pharmaceutical industry started to employ a systematic way to innovate, carried out by the use of random screening methodology (Schwartzman, 1976; Gambardella, 1995). This technique consists of testing all possible molecules endlessly in the search for the desired therapeutic effects (Grabowski; Vernon, 1982; Gambardella, 1995; Schwartzman, 1976). Random screening combines empiricism to scientific advances, this technique reach its peak between the 1940s and 1950s generating excellent results due to the number of NCE (see figure 1 on pg. 4)(Achilladelis; Antonakis, 2001).

The random screening success enabled the development of antibiotics and antihistamines, which were the set of chemistry-based innovations that defined the industry in the 1930s (Achilladelis and

Antonakis, 2001). Although highly laborious and empirical, the results obtained through random screening outweighed any economic cost within this technique (Gambardella, 1995 Schwartzman, 1976; Vernon and Grabowsky, 1982). The whole process had the principle of a "roulette" with a high success rate (Nightingale *et al.* 2007). But, in the 1960s, this methodology started to show some exhaustion, and, therefore, productivity declined (Schwartzman, 1976; Grabowsky and Vernon, 2000; Nightingale, 2000; Nightingale *et al.* 2007; Gambardella, 1995; Vernon; Grabowsky, 1982). To solve the drop in random screening's productivity, companies sought to increase the efficiency of other drug discovery methods (Nightingale, 2000), but, still, based on chemistry related competences, following a well succeeded trajectory that had already enabled the random screening to be successful.

By further developing the industry' pharmaceutical core competencies, the technological trajectory followed a path which narrow the potential candidates through the construction of better hypothesis on how the new compounds would attack the disease (Gambardella, 1995; Amzel, 1996; Bohacek *et al.*, 1996). The technological evolution was focused on reducing the empirical factor of past techniques and, as consequence, increase the rationality in the innovative process. This new technique could be addressed in several ways as: discovery by design (Gambardella, 1995) or rational drug design. In sum, they are a rational approach for drug design. This new set of technologies, in the drug discovery activity, is exemplified by the structured base design (SBD) technique (Amzel, 1996, Bohaeck et al. 1996, Gane and Dean, 2000; Schwardt *et al*., 2003).

In this context, the answer sought by pharmaceutical companies was to develop ways to design a "perfect" molecule for the desired purposes, instead of randomly test numerous candidates. The SBD encompasses several techniques in order to build a component for the needed purposes, for that the molecule is designed to bind perfectly to a protein. Therefore, in a rational design approach, the ability to build better drugs relates, closely, to the understanding of how chemical receptors bind and the structure of target (Amzel, 1998). Therefore, SBD has a simple logic, first the target needs to be identified. Second, the target structure defines how a new molecule must be designed. Finally, theoretically, the engineered molecule would bind in the desired target.

In order to design and discover the target structure some techniques are needed, being X-ray crystallography and Nuclear Magnetic Resonance (NRM) the most successful ones into discovering the target structure (Amzel, 1998; Gane; Dean, 2000; Schwardt *et al*., 2003). In addition, there are docking techniques composed by computer algorithms that allow to test if the molecule can bind to the target, being it a *in silico* technique (Gane; Dean, 2000). The SBD relies on computer models (docking) for testing and designing molecule structures, but these models are not capable of dealing with several complexities that emerge from biding problems. Therefore, many computer tested molecule could not work in reality or could work in reality but not at the computer models (Gane; Dean, 2000).

All those techniques show an interesting fact, they are all derived from competences related to chemistry and physics principles, we may call them pure pharmaceutical technologies. None of these techniques are based on the molecular biology knowledge base, in that sense, they are not biotechnologies. Therefore, the SBD is a solution within the scope of the pharmaceutical industry knowledge base. Based on that, pharmaceutical technologies have impacted the industry innovation output at its beginning. Therefore, in a time perspective analyses our hypothesis is:

H1: Pharmaceutical technologies had a positive effect on technological outputs at the short run.

1.2 The use of biotechnologies competences for R&D techniques

In a recent period, biotechnology has brought a new impetus to R&D through various ways of searching for new drugs and further expanding the research scope of pharmaceutical companies.

Biotechnologies dedicated to the pharmaceutical industry are a series of techniques that span out from the molecular biology scientific base. The discovery of the double helix by Watson and Crick in 1953 was "the triumph of molecular biology and the signal that it had arrived as a discipline". (Kenney, 1987, pg. 19). The first step into the establishing of a biotechnology-based industry was given

in 1974 by the possibility of transferring organism's genetic material through plasmids[1]- the Cohen-Boyer patents-, rather than using special types of virus. This technique was considered "(…) the simple pivotal event in the transformation of the 'basic' science of molecular biology into an industry" (Kenney, 1987, pg. 23). Thus, techniques based on molecular biology enable the genetic alteration, introduction of genes into organisms and ability to divide and to construct DNA sequences in vitro (Martin, 1999).

One of the promising advances in the field of research with extraordinary outcomes to biotechnology was the Human Genome Project (HGP), a significant research effort, undertaken from 1991 to 2003. The HGP aimed to decode the human genetic sequence. This research effort was a milestone in how biotechnology could be useful for the pharmaceutical industry (Macarron, 2011; McKelvy; Orsenigo, 2001; Quéré, 2004). As an outcome, the HGP enable the opportunity of exploiting, economically, compounds that directly affect the interactions between genes expressions and the manifestation of diseases and, therefore, change the way diseases were diagnosed and treated (McKelvey; Orsenigo, 2001; Quéré, 2004).

As a research effort that allows the creation of a new set of technologies, the HGP has established the infrastructure in which molecular biology dedicated to genetic was linked into solving important aspects of pharmaceutical industry problems (Martin *et al.*, 2011).

There is still doubts about the role of biotechnology as a new paradigm or as a set of technologies dedicated to discover drugs on a small molecule paradigm. We assume, based on: Henderson *et al.* (1999), Drews (2003), Gisling; Noteboon (2006); Hopkins *et al*. (2007, 2013), Kong; Li; Zhang (2009); Nightingale; Madhi (2007), Pereira; Williams (2007) , Nightingale(2000), that biotechnology is nowadays a tool – or methodology – for new molecules discovery with, a possible, high rate chance of creating active components.

Biotechnology enables the use of new research technologies in addition to those already in use by the pharmaceutical industry. Thus, biotechnology as a new methodology can increase the pharmaceutical industry ability to generate possible candidates for new components (Gisling; Noteboon, 2006; Nightingale, 2000; Nightingale; Madhi, 2007; Powell *et al.*, 1996; Santos, 2003).

The use of biotechnology means that the drug discovery activities are relying even more on biotechnology competences as this search activity evolves. "So the drug discovery underwent a change towards molecular biology computing and genomic science in recent years." (Schimid *et al.*, 2001, pg 42).

Through biotechnology the discovery activities have acquired a larger scale into screening molecules. The High Throughput Screening (HTS) is one of the most prominent biotechnology and it has increased, significantly, the capacity of enterprises to screen new compounds through standardizing and automatizing certain features, like sample size (Nigtingale, 2000; Pereira; Williams, 2007).

The HTS is, basically, the automation of random screening through biotechnologies enabling companies to test more components in a very short time (Nightingale, 2000; Hopkins *et al* 2007, Pereira and Williams, 2007). According to Houston and Banks (1997) before HTS an enterprise could possibly check 75000 components of the same class for 20 targets. The HTS allowed testing a million components, within a class, for 100 targets. The HTS was a breakthrough among techniques to test components. It is a technology that increased the scale in the drug discovery process, as it enhances the number of candidates for new medicines. From 66 published clinical candidates (molecules) at the Journal of Medicinal Chemistry, 29% of them were discovered through HTS, making it one of the most effective form of discovering new compounds (Brown; Boström, 2018).

The extensive use of HTS, generating good results, and the dedicated teams specialized on running this technology (Macarron, 2011; Pereira; Williams, 2007) has created a new R&D path based on biotech competences. Those technologies follow a distinct logic in comparison to rational drug design approach (Amzel, 1996; Macarron et al., 2011; Willians; Pereira, 2007). Whereas, the structure base design looks to construct a specific molecule for a desired target; the HTS enables the pharmaceutical industry to screen several known compounds in order to find some therapeutic effect. One technique follows a rationalization path, while the other increases the experimentation scale

[1]Plasmids are DNA molecules capable of reproducing chromosomal DNA independently.

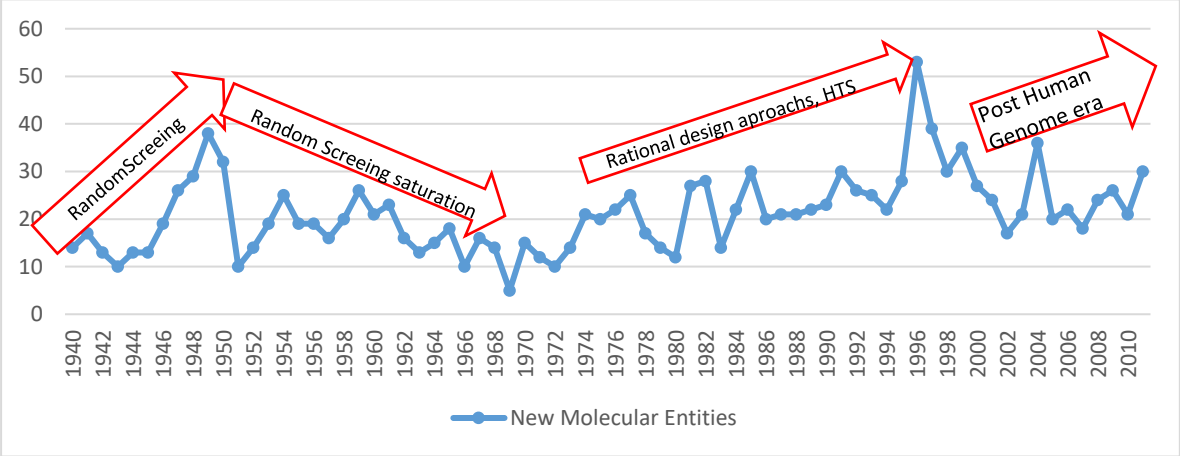
allowing the pharmaceutical industry to test more molecules in less time (Gane; Dean, 2000). Therefore, our second Hypothesis, considering a time perspective, is:

H2: Biotechnologies have a positive effect on technological outputs at the long run.

Both biotechnologies and pharmaceutical technologies were impacted by the information technology revolution. For us, this impact spreads all over the industry. On one hand computer simulations (docking techniques) are used for rational drug design; on the other hand, the database management techniques are used for controlling enormous molecule libraries acquired through HTS. Therefore, we will not create a hypothesis on the Information technology, but in this study, we use it as an exogenous variable (see methodology).

In sum, all the main technologies and the NCE approved by year are presented in the graphic bellow.

Figure 1: New molecular entities approved by the FDA over the years and the main technologies used for drug discovery



Source: Matos, 2016, pg 39

This graph combines technology and its outputs over the years, but the correlations will be evidence in the following sections.

2 Methods

This article relies on time series models for evidencing our hypothesis. For that we begin presenting the time series used. Then, we build a Vector Autoregressive Model (VAR) in an attempt to look for stationary processes and short run analyses. Finally, in the presence of a cointegration we conduct a Vector Error Correction (VEC) model enabling short and long run analyses.

2.1 Data

This article comprises four half-yearly time series, ranging from 1980 to the first semester of 2014, totalizing 70 observations. The number of observations surpass the minimum necessary for conducting any type of time series analyses (Enders, 2014). The series used are the: (i) natural log of New Chemical Entities; (ii) natural log of pharmaceutical patents, (iii) natural log of biotech patents and (iv) natural log of information technology patents. Bellow we present the series in more detail.

New Chemical Entities (NCE) are the pharmaceutical industries' innovative output. Broadly all NCE are compounds that goes through animal and human population tests (clinical trials)[2] and are

[2] For more details about the steps and the typical clinical trial characteristics, please see: Gambardella, 1995,

approved by the FDA to become new drugs. We conduct a log transformation on number of NCE approved by the FDA on a half-yearly base. The number of NCE was retrieved at the FDA[3]. There we obtained all approvals of New Drug Applications (NDA) and Biological License Application by month. The NDA encompass, majorly, small molecules being a chemistry based pharmaceutical output and BLA are large molecules, essentially biotech outputs. After retrieving all approvals, we compile only the New Chemical Entities submission[4].

Pharmaceutical patents (Pharm) are the patents that comprise chemistry related input in the innovative process. For that we conducted the log transformation on the number of patents issued at the United Sates Paten Class system (USPC) 514 and 424. The patent class definition follows Hall, Jaffe, Trajtenberg (2001) patent-based sector classification sector. The data was retrieved from the PatFT (Patent Full-Text and image database), a free access database from USPTO where we could search patents according to their classes.

Biotechology patents (Bio) are the patents linked to molecular biology related input in the innovative process. We conducted a log transformation on the number of patents issued at classes 535 and 800 from USPC. The patent class definition follows Hall, Jaffe, Trajtenberg (2001) patent-based sector classification sector. The patent data retrieved from the PatFT.

Information technology patents (info) are an attempt to encompass all patents related to group of information technologies that impact the pharmaceutical industry technologies. We use the series as an exogenous variable due to these technologies' pervasiveness. For that we conducted the log transformation on the number of patents issued at classes 41, 380, 382, 395, 700, 701, 702, 704, 705, 706, 707, 708, 709, 710, 712, 713, 714, 360, 365, 369, 711. The patent class definition follows Hall, Jaffe, Trajtenberg (2001) patent-based sector classification sector, but in order to encompass the main information technologies we combine computer&hardware patents to information storage patents. ı

Bellow we summarize the data in a table and present the series graphically and the data descriptive statistics.

Schwartzman, 1976, FDA 1990; 1999. The clinical trial are also describes at: www.clinicaltrials.gov and www.fda.gov

[3] https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

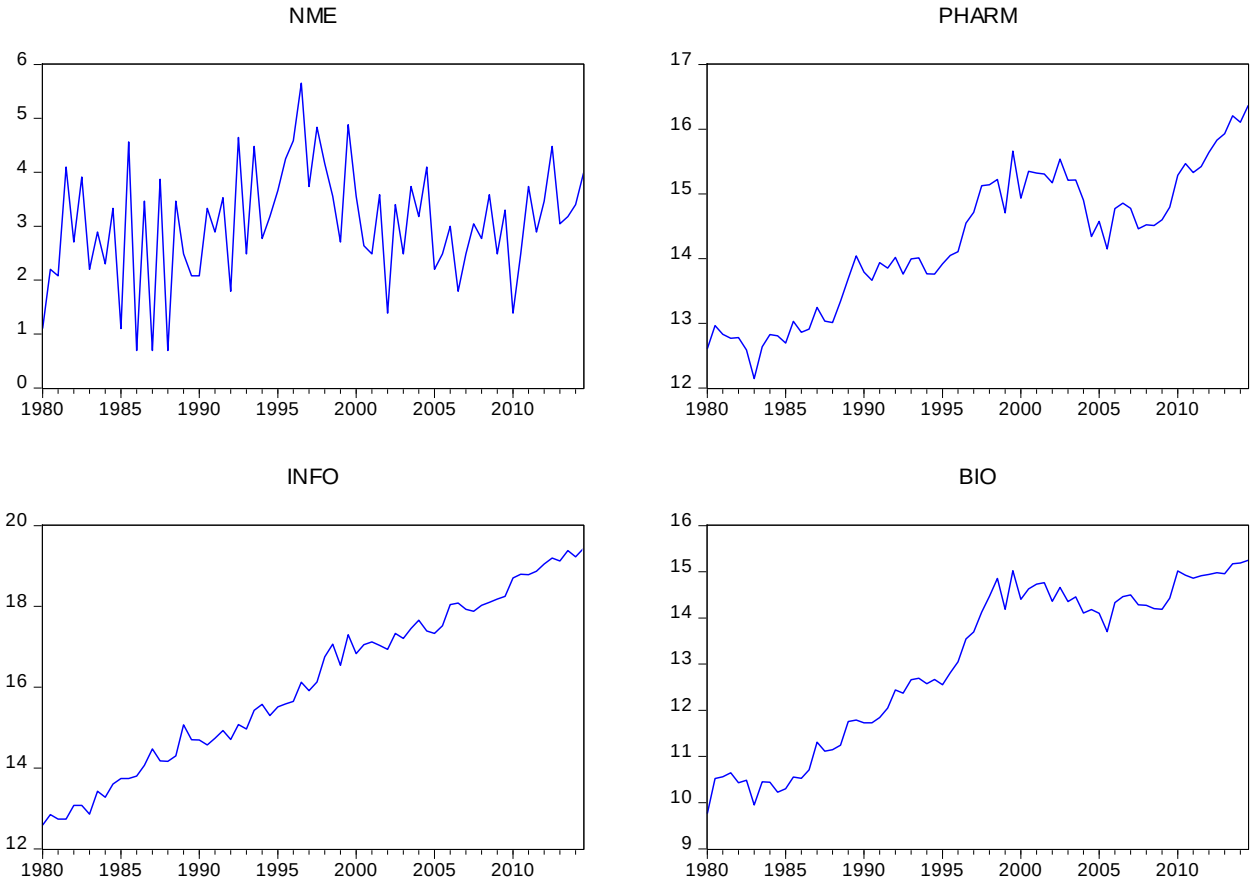
[4] We needed this separation because the FDA classifies both NDA and BLA submissions in 10 types, for a better comprehension on the FDA classification types see: https://www.fda.gov/media/94381/download.

Table 1: Variables

Series	Description	Period	Source
NCE	Natural log of New chemical entities approved by the FDA	Half-yearly serie from 1980 to the first half of 2014	FDA
Pharm	Natural log of issued patents from class 514 and 424 at USPTO	Half-yearly serie from 1980 to the first half of 2014	PatFT (USPTO)
Bio	Natural log of issued patents from class 535 and 800 at USPTO	Half-yearly serie from 1980 to the first half of 2014	PatFT (USPTO)
Info	Natural log of issued patents from classes 41,380,382,395,700,701,702,704,705,706,707,708,709,710,712,713,714, 360, 365, 369, 711 at USPTO	Half-yearly serie from 1980 to the first half of 2014	PatFT (USPTO)

Source: own elaboration

Figure 2 – Series transformed in natural logarithm (LN)



Source: own elaboration

Table 2- Descriptive Statistics

	BIO	INFO	PHARM	NME
Mean	13.033	16.099	14.277	3.041
Median	13.699	16.128	14.400	3.111
Maximum	15.250	19.437	16.367	5.652
Minimum	9.764	12.591	12.143	0.693
Std. Dev.	1.747	2.032	1.069	1.061
Skewness	-0.410	-0.077	-0.095	-0.194
Kurtosis	1.646	1.792	1.982	2.890
Jarque-Bera	7.308	4.324	3.125	0.472
Probability	0.026	0.115	0.210	0.790
Sum	912.332	1126.935	999.400	212.864
Sum Sq. Dev.	210.497	284.841	78.784	77.605
Observations	70	70	70	70

Source: own elaboration

By looking at the graphics we suspect that all series all non-stationary. Nevertheless, this conclusion must be achieved through unit roots test.

2.2 The VAR Model

In order to evidence the contribution of biotechnologies to the production of NCE we depart from a Vector Autoregressive Model (VAR)[5] composed by a set of *K* endogenous variables, given by the vector $y_t: \{y_{1t}, y_{2t}, \dots, y_{Kt},\}$, and a set of *M* exogenous variables given by $x_t: \{x_1, x_2, \dots, x_S\}$. Therefore VAR(p) is represented by following equation:

$$y_t = A_0 + A_1 y_{t-1} + A_2 y_{t-2} + \cdots + A_p y_{t-p} + B_s x_t + \varepsilon_t \quad (1)$$

Where, A_0 is the intercept vector; A_i is a matrix of K x K parameter for i = 0, ... , p; B_j is a matrix of K x M coefficients where $j = 0, \dots, s$ and x_t is a vector of M x 1 exogenous variables; ε_t is a non-correlated white noise K x 1vector, therefore $\varepsilon_t \sim i.i.d.(0; I_k)$.

The VAR (equation 1) is conditioned to the series stationarity in time. Therefore, the first step into modeling is to confirm the series stationarity through unity root test.

2.2.1 Unit Root Test

In macroeconomic studies the non-stationarity of most common series, like: GDP, wages, nominal exchange rates, among others, is well-known. Nevertheless, within economics of innovation, stochastics processes leading to innovation aren't a relevant premise, many cornerstone studies in special Nelson; Winter (1982) consider any process of technical change as a non-stochastics process. For that, this article adds one contribution, within innovation studies, by using time series and, therefore, indicating innovation, at least in the pharmaceutical industry, as a stochastic process.

We use the *Augmented Dickey-Fuller (ADF)*, the *Phillips-Perron (PP)* the *Kwiatkowski-Phillips-Schmidt-Shin (KPSS)* as unit roots tests. Both ADF and PP have the same hypothesis but the KPSS has different ones, as showed next:

[5] For further details see: ENDERS (2014).

Table 3: Unit roots test's hypothesis

Test	H_0	H_1
ADF and PP	$\exists$ *Unit root and the serie is stationary*	$\nexists$ *Unit root and the serie is not stationary*
KPSS	$\nexists$ *Unit root and the serie is not station*	$\exists$ *Unit root and the serie is station*

Source: own elaboration

First we conduct the tests for the series at level. As expected all series were non-stationary at 1% significance, except the NME series.

In order to advance the series analyses we conducted the unit roots test for all series in first difference. We expect that the first difference will eliminate the tendency making them stationary. In addition, if stationary at first difference we can identify the series order.

Table 4: Unit root test (ADF, PP, KPSS) for the series in first difference

Test Type		Significance Level	Critical value	t-Statisitics			
				NME	*Pharm*	*Bio*	*Info*
Augmented Dickey-Fuller (ADF)	INTERC	1%	-3.53	-7.82	-11.64	-11.74	-7.40
		5%	-2.90				
		10%	-2.59				
	TREND AND INTERC	1%	-4.10	-7.72	-11.59	-11.68	-7.37
		5%	-3.48				
		10%	-3.17				
	NONE	1%	-2.60	-7.88	-11.23	-5.54	-2.12
		5%	-1.95				
		10%	-1.61				
Phillips-Perron (PP)	INTERC	1%	-3.53	-29.91	-11.64	-11.61	-31.13
		5%	-2.90				
		10%	-2.59				
	TREND AND INTERC	1%	-4.10	-29.68	-11.59	-11.55	-32.29
		5%	-3.48				
		10%	-3.17				
	NONE	1%	-2.60	-29.98	-11.03	-10.49	-10.38
		5%	-1.95				
		10%	-1.61				
Kwiatkowski-Phillips-Schmidt-Shin (KPSS)	INTERC	1%	0.739	0.118	0.082	0.153	0.395
		5%	0.463				
		10%	0.347				
	TREND AND INTERC	1%	0.216	0.100	0.080	0.058	0.419
		5%	0.146				
		10%	0.119				

Source: Own Elaboration.

As expected all series are stationary. The critical values at the ADF and PP are lower that the calculated t-statistics. In the case of KPSS the critical values are greater than the t-statisics. The only exception is the info, considering trend and intercept, in the KPSS test. Nevertheless, we can sustain the stationarity, in first difference, based on the ADF and PP.

We conclude that all series are non-stationary integrated of order 1 –I(1). Therefore, we transform the data in order to conduct a VAR model (eq. 1). Unfortunately, VAR estimations allow only short run analyses (Enders, 2014). As discussed in in the literature the impact of biotechnologies is presumed to be a long run process. This makes VAR estimations an inadequate choice based on our hypothesis.

One possible way to conduct a long run analyses is to search for, at least one, cointegration among the series, enabling us to conduct the adequate estimation and, therefore, conduction a long run analyses (ENGLE; GRANGER, 1987). The cointegration will allow us to conduct a Vector Error Correction (VEC) model.

2.2.2 Cointegration analyses

The search for cointegration among the information system in our innovative indicators is not an end in itself (JOHANSEN, 1988). This is a "modern" and few explored application in innovation studies that intends to identify long run effects at the NCE determinants.

According to JOHANSEN (1988) the presence of just one cointegration is a sufficient condition for the existence of linear stochastic tendencies between the series used. This condition forces a correction in the VAR equation (1) making it a Vector f Error-Correction Model (VECM). Basically, this correction is to put the whole model in a first difference and create an *Error Correction Vector*, as shown bellow:

$$\Delta y_t = \Gamma_1 \Delta y_{t-1} + \cdots + \Gamma_{p-1} \Delta y_{t-p} + \Pi y_{t-p} + \Phi D_t + \varepsilon_t \quad (2)$$

Where, $\Gamma_i = -(A_{i+1} + \cdots + A_p)$ for i=1, 2,...,p-1 and $\Pi = \alpha\beta' = -(I - A_1 + \cdots + A_p)$.

The α parameter is a matrix that represents the speed of adjustment of parameters at the short run. β is a cointegration coefficient matrix between the variables at long run. Being both the parameters and matrix of length n x r in which n is the number of variables and r is the number of vectors in the cointegration matrix Π.

In order to test for cointegration, first we have to choose the lags based on a Irrestricted VAR. The lags were chosen based on the following information criteria:

Table 5: Lag selection according to information Criteria

Criterion	Order
AIC	2
HQ	2
SC	1
LR	2
FPE	2

Source: own elaboration

Base on the results we adopt 2 lags.

After selecting the lags we conduct the Johansen test for cointegration. There are five possible models of cointegration to be used (JOHANSEN, 1995), the chosen one is given by rank tests. Based on the Akaike Information Criteria by Rank and the Schwarz criteria we chose the model that contains the intercept at the cointegration vector and linear tendency at the cointegration vector and level.

The Johansen test is presented in the table bellow:

Table 6: Johansen methodology for cointegration test

Test	Hypothesis	Eigenvalue	Statistic (λ)	Critical Value	Prob.*
Trace	r = 0	0.44	53.14	42.92	0.00
	r≤1	0.16	14.10	25.87	0.65
	r≤2	0.04	2.61	12.52	0.92
Maximum Eigenvalue	r = 0	0.44	39.03	25.82	0.00
	r≤1	0.16	11.49	19.39	0.46
	r≤2	0.04	2.61	12.52	0.92

Source: Own elaboration
*Null Hypothesis at 5% of significance.

The p-value for the Maximum Eigenvalue and the trace test indicate the presence of at least one cointegration allowing the use of VECM. Therefore, we conducted the VECM in order to look for short and long run analyses. The results are discussed in the next section.

3 Results and Discussion

The VECM equation containing the coefficient estimations follows:

$$\Pi_{t-1} = 1.000NME_{t-1} - \underset{\substack{(0.75965)\\[-1.07248]}}{0.815Pharma_{t-1}} - \underset{\substack{(0.58093)\\[-2.46859]}}{1.434Bio_{t-1}} - \underset{\substack{(0.0803)\\[-4.63274]}}{0.372info_{t-1}} + 40.490 \quad (3)$$

standart deviation ( ) and t value [ ]

The estimations for the long run equations in the VEC model allow us to identify a positive (+ 1.434)[6] and significant at 1% (t = -2.469) relation between NCE and Bio. Therefore, biotechnologies have a positive effect, in the long run, at the NCE, proving H2. We stressed that all signals were expected.

Our results corroborate the qualitative studies in the literature review. The recent development of biotechnologies and their systematic use for discovering new medicines only began after the Cohen-Boyer patents. So, their impact could only be observed in the long run, more interesting, we saw the lack of impact from Pharma patents. Therefore, our results are in line with Brown; Boström, 2018.

The VECM also allows to observe short run impacts. Table 6 shows the main short run impacts at 5% significance level.

[6] In VECM models the signals are changed. Therefore, positive sign means negative effects and negative signs means positive effects.

Table 7: Short Run Estimations

Variable	Coef.	Standard errors
Π	-0.1254*	0.092
ΔNME_{t-1}	-0.735***	0.087
$\Delta Pharm_{t-1}$	0.604	0.696
ΔBio_{t-1}	-0.757	0.706
const	11.056*	7.828
$Info_t$	-0.678*	0.482
R^2		0.651
Observations (n)		68

Source: Own elaboration
***sig. a 1%.
**sig. a 5%.
*sig. a 10%.

In the short run, only the past year NCE have a significant effect at the actual NCE. This fact shows cumulativeness effect on new NCE. The other variables: $Pharm_{t-1}$, Bio_{t-1} and $Info_t$ were not significant, therefore we do not confirm H1. Even though being not significant (at least at 5%), $info_t$ had positive impact, as we expected.

The impact of previous NCE on future NCE is a very similar result to the one of Brown; Böstrom (2018). These authors have analyzed 66 published clinical candidates and the methods used to "discover" them. As result, Brown; Böstrom (2018) show that the 43% were based on already known compounds. Our results are much broader, because they encompass all NCE issued at the US, in addition, we are evidencing an industry strategy of utilizing past compounds to generate new ones.

Nevertheless, the short run findings prove a relevant neo-shumpeterian hypothesis regarding cumulativeness in the innovation process. In essence our model proves, in short run, the impact of past knowledge.

This article analyses have long been the subject of cornerstone studies (such as: Pakes; Griliches, 1980; Hausman; Hall; Griliches, 1984; Griliches, 1998). In fact, we analyze the role of knowledge, more precisely, we, as Griliches, were looking for the additions on useful knowledge made by patents (Griliches, 1998). This subject was not forgiven, much less, solved. Recent studies are looking at this same question in various ways, for example: Mokyr, 2002; Cowan; David; Foray, 2000; Nelson, 1999; Foray; Hargreaves, 2003. In sum, we could shed light on the subject of useful knowledge.

In the pharmaceutical industry, this can be better observed and calculated due to the industry dynamics. We can assure that NCE are useful knowledge, they represent candidates that surely will become new drugs and patents measure more than useful knowledge.

Our article indicates a relevant process that can be understood in a time perspective. In the long run Biotech patents have impact over NCE. Therefore, these patents impact are observed in the future, after they go through several selection environments, for then being able of impact NCEs. So, patents take time to be "part" of NCEs. In the short run, the already selected knowledge (the NCE) are much more useful than patents. Therefore, we were able to answer an extremely relevant question: the impact of patents in useful knowledge.

Conclusions

In this article we try to prove two hypothesis: H1- Pharmaceutical technologies had a positive effect on technological outputs at the short run and H2- Biotechnologies have a positive effect on technological outputs at the long run.

We consider biotechnology as new set of technologies highly used in the pharmaceutical industry in order to improve their innovative process. The systematic use of biotechnologies is relatively new when compared to the industry' age.

In order to prove our hypothesis, we conduct a VECM model. Our data was fully suited for that analyses, we had 70 observations from 1980 to 2014. The model has allowed us to prove H2. Although the pharmaceutical variable was positive, it was not significant in the long run. Perhaps, on the one hand, it can be explained by the period of our sample because it favors the increase in biotechnological applications. On the other hand, the decline use of random screening process could be caused by the rise of biotechnology, thus affecting the impact of pharmaceutical patents on NCE. For this reason, we have had no conclusive results in this regard, and will be referred for another investigation.

One interesting result that goes beyond our hypothesis was the impact of past NCE in new ones. The short run effects have consistently show past NCE as the only significant variable on explaining future NCE. This fact is an interesting conclusion among the studies of Innovation because it proves and show cumulativess in the innovation process.

Despite the conclusion about the industry as a whole. This article allowed us to explore an interesting element among the innovation studies. Due to the industry dynamics the impact of patens in NCEs are also the impact of patents at the useful knowledge. This subject was long posed by studies conducted by Griliches, but it is still an extremely relevant subject due to several problems that a Neo-Schumpeterian knowledge theory have in explaining and measuring the real impact of knowledge over innovation.

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