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Diffusion of new drugs: a review on the available empirical evidence focused on developing countries

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Abstract

The current paper is aimed at reviewing the available empirical evidence on the variables that affect the diffusion of new drugs, especially in developing countries. The review describes the scientific literature available on CAPES, ECONPAPERS, Google Scholar, ISI Web of Knowledge, NBER, and SciELO's databases. The papers revised were divided into two categories: studies on diffusion based on the empirical literature focused on a particular variable and those of empirical nature that mostly use diffusion models (econometric or simulating models). It was found that the papers reviewed presented a diversity of objectives and methodological procedures, although they were generally based on the mainstream of economic thought. The most common variables, found in the survey, related to diffusion are: patients' socioeconomic status and education level; network effects of information; health insurance-plan characteristics; severity of patient disease; clinical practice (physician's prescription); intellectual property rights; regulatory environment; and market characteristics.

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INTRODUCTION

The concept of diffusion of an innovation has been taken from the classical definition of Everett M. Rogers, as a process through which an innovation (an idea perceived as new) is communicated through certain channels for a period of time among the members of a social system (ROGERS, 2003). Within the pharmaceutical sector, an innovation can be defined as a technological advancement that leads to the creation of a new drug or to the improvement of the therapeutic value of an existing one. Therefore, an innovation can lead to new active substances, to new indications of the existing products, or to new ways of handling the same product. All those three kinds of innovation may, in principle, present a significant value to the patients (WILSDON; NITSCHE, 2004). Among other aspects, the importance of new drugs' diffusion can be evaluated by its positive impacts on the health indicators. For example, both, increase of global life span or reduction of infantile mortality are strongly related to technologies' diffusion and medical information (PRESTON, 1996; JAMISON et al, 2001; PAPAGEORGIU et al, 2007).

It's well known that particularities in healthcare, in its different levels make the diffusion of new technologies, including new drugs, to assume very peculiar characteristics. Such statement is also appropriate to the characteristics of the pharmaceutical market, to the regulatory environment, and to the intellectual property regime; and, mainly when it refers to the aspects that differentiate the market of the developed and developing countries. Among the characteristics that distinguish the latter ones, it can be mentioned: small markets[1], epidemiologic pattern in which contagious diseases are predominant, a deficient system of health attention and an ineffective regulatory system. (KREMER, 2002). All these aspects, as it will be seen, are relevant to the process of new drugs' diffusion.

The developing countries cope with a disease environment remarkably different from the developed ones, due to their poverty as well as their geography. Contagious diseases (e.g. tuberculosis, HIV/AIDS) and parasitic diseases (e.g. malaria) affect mostly low income

[1]In 2007, according to data from the IMS Health only North America and Europe were responsible respectively for 45,9% and 31,1% of the pharmaceutical global sales, totaling 70%. The rest 30% of the world sales were spread this way: Asia, Australia e Africa (9,4%), Japan (8,8%) e Latin America (4,8%).

countries, while high income countries present higher occurrence of non-communicable diseases, like cancer and cardiovascular diseases. (KREMER, 2002).

WHO (2001) presents a taxonomy of diseases considering the aspects related to the countries' income. According to such criteria, diseases of Type I would be the ones existing in rich and poor countries, with a big number of vulnerable populations in both (e.g. diabetes and hepatitis B). In this case market mechanisms would be capable of generating R&D investment and industrial production of drugs and vaccines in a way that for this kind of diseases there wouldn't be any lack of medicaments. Restrictions on their access would be a matter of income. Diseases of Type II, on the other hand, can also be found in rich and poor countries, however mostly in the latter ones. (e.g. tuberculosis, HIV/AIDS). In this case, R&D investments do take place, although below the necessary (mainly for the diseases that are more frequent in low-income countries). The big problem of low-income countries would be related to diseases Type III (Trypanosomiasis and Leishmaniasis) that occur almost exclusively in these ones. Economic incentives for investment in R&D and production of new specific drugs for such group of diseases are very scarce, almost non-existing.

WHO (2001)'s taxonomy – which considers, within the pharmaceutical industry, that R&D efforts and drug production vary, in a certain way, as a function of the income in the target markets – would be, therefore, in accordance with GAP 10/90, a statistical evidence of the Global Forum for Health Research which acknowledge that only 10% of the world expense in R&D directed to diseases that affect, mainly, 90% of the world population. This "scientific deficit" is translated, consequently, into a high inequality, at least concerning treatment availability. From the 1,233 licensed medicaments worldwide between 1975 and 1997, only thirteen were target to tropical diseases (KREMER, 2002). Among the 15 leading therapeutic classes in sales, in 2008 there were oncological products, fat regulators, breathing and a-diabetic agents. Together they were responsible for almost 20% of total sales, according to data from IMS Health (2009) – there were no product focused on Type III disease treatment on that list.

This article's objective is to revise the available empirical evidence on the variables that affect the diffusion of new drugs, especially in developing countries. In that sense, the work is focused mainly on the empirical literature, although theoretical aspects may arise as the

discussion takes place. Therefore, the results will be highlighted as well as the methodological procedures used by the referred authors.

In order to proceed the investigation, a review was made to describe the scientific literature available at CAPES, ECONPAPERS, Google Scholar, ISI Web of Knowledge, NBER and SciELO databases, through a simplified research by indexing search words on the title, abstract or key-words (Adoption; Diffusion; new drugs; new pharmaceuticals; developing countries; pharmaceutical industry; and their analogous in Portuguese and in Spanish). Relevant works having theoretical or empirical approach were also included. However, the available literature on the diffusion of new drugs is very scarce, particularly in developing countries. Such fact was pointed out by Vakratsas e Kolsarici (2008), Berndt *et al* (2007) and Lanjouw (2005), besides other authors.

DIFFUSION OF NEW DRUGS: EMPIRICAL EVIDENCES

The literature review allowed the identification of factors related to the process of new drugs diffusion in eight specific categories following their frequency , in most empirical works: (a) patients' socioeconomic status and education level (see, e.g., GOLDMAN; SMITH, 2005); (b) network effects of information (e.g., PAPAGEORGIU et al, 2007; BERNDT et al, 2003; BERNDT et al, 1999); (c) health insurance-plan characteristics (e.g., CROWN et al, 2004); (d) severity of patient disease (e.g., CONG, 2009; VALENSTEIN et al, 2006); (e) clinical practice (physician prescription) (e.g., VAKRATSAS; KOLSARICI, 2008; FOOTE; ETHEREDGE, 2000; STEFFENSEN et al, 1999); (f) intellectual property rights (e.g., LANJOUW, 2003; BORRELL, 2003; (g) regulatory environment (e.g., ATUN; GUROL-URGANCI, 2007); (h) and market characteristics (e.g., VAKRATSAS; KOLSARICI, 2008; DESIRAJU et al, 2004; KREMER, 2002).

According to the literature reviewed, the investigation of the variables that affect new drugs diffusion can be divided into two groups. The first one refers to works in which the research is based on the review of empirical texts focused on a particular variable; for example, Atun e Gurol-Urganci (2007), who compiled studies about the role of regulation on the diffusion of pharmaceutical innovations in health systems; or Lanjouw (2003), who discussed the relation between intellectual property and the availability of pharmaceutical products in poor countries. The second group deals with empirical works that mainly use econometric or

simulating models, which are more common, and diffusion models ("natural" or planned), such as VAKRATSAS; KOLSARICI, 2008; DESIRAJU et al, 2004; BERNDT et al, 1999; STEFFENSEN et al, among others. The application of such models on drugs diffusion can be seen in FERRENCE, 2001.

The empirical findings of the revised papers were grouped by identified variables categories (above mentioned) that affect the diffusion. This article has mainly an empirical interest, so the aspects highlighted are data, research method, and results. Obviously the empirical findings on the different texts studied are not directly comparable. This is due to the fact that they are remarkably different regarding objectives and investigation method, although part of them has similarities, e.g., by using diffusion models. In this way, the discussion on the literature will be limited mostly to the description of the findings. The most common characteristic observed on the empirical works reviewed was the fact that they are tied to theoretical/empirical postulates of the mainstream, economic thought or to the neoclassical theory, which supposes the maximization and equilibrium models. The papers that deal with developing countries will be emphasized, since they are object of the interest of this study. However, the scarce literature, focused on this group of countries concentrates frequently on the diffusion aspects linked to factors such as intellectual propriety rights and market characteristics.

Patients' socioeconomic status and education level (a)

Very little is known on the mechanisms through which education can affect health. One of the possibilities pointed out by the literature is that more educated individuals have higher possibility of adopting new medical technologies – including drugs (LLERAS-MUNEY; LICHTENBERG, 2002; GLIED; LLERAS-MUNEY, 2003). Lleras-Muney and Lichtenberg (2002) have tried to investigate such possibility, by an econometric model on the probability of more educated individuals make use of new drugs more frequently. Data related to drug consumption under the physician's prescription from the Medical Expenditure Panel Survey (MEPS) for the year of 1997 were used. This database was built up from a survey that contains non-aggregated data on the demographic characteristics (such as age, gender, race, education, income, etc.), on health plan status (insurance status) and on drug use (including drug price, who paid for it, condition in which it has been taken). Data were taken at user's level. The sample was limited to individuals over 25 years old that have used at least one medicine under prescription in 1997. Concerning the data on new drugs approved for use, the

U S Food and Drugs Administration (FDA) made the source of information available. As result, Lleras-Muney and Lichtenberg (2002) confirmed their hypothesis. In other words, more educated people have higher probability of using drugs for a certain condition, suggesting that such individuals are more capable of learning with experience.

According to Goldman e Smith (2005), new medical technologies are a big promise to improve the population's health, however they raised some concern regarding the expansion of health differences, which are already high, related to the socioeconomic status of the patients (socioeconomic status - SES). Those authors argue that the impact of a new technology on the health disparities does not depend only on how difficult it is to adopt it, but also on who is submitted to the treatment. So, if new effective medical technologies are rapidly adopted by more educated patients, SES health disparities can initially grow, although people's health in groups of lower SES can eventually be improved. In order to test this hypothesis, Goldman and Smith (2005) examined, based on three prominent medical investigators[2], the diffusion of new drugs for hypertension treatment (ACE inhibitors and calcium channel blockers) for the last 25 years. Nevertheless, they didn't find evidences that the diffusion of these drugs within the medical practice have favored higher SES groups in sacrifice of lower SES groups. In summary at least for the antihypertensive- analyzed they admitted that in relation to new medical technologies diffusion, the socioeconomic status of the patients is not a determining factor for the increase on health disparities.

The survey data used were obtained from studies carried out in the USA. The initial hypothesis stated that educational level, an important variable of socioeconomic differentiation, is associated to the patients adherence to new treatments, in favor of the better educates ones, causing disparity in the use of medicines and in the population health. Therefore the methodological strategy was to estimate the variables associated to the use of high blood pressure and to verify its influence on educational level. A linear regression model was used applying values of independent variables such as age, gender, marital status, educational levels, mean cholesterol, blood sugar and weight/height index, and a quadratic time trend to observe changes in the percentage of the population using anti hypertensive medicines, the dependent variable. To observe if the diffusion velocity of new drugs were modified by educational level, interactions were tried on quadratic time trend and education dummies. The results did not

[2] Framingham Heart Study (FHS); National Ambulatory Medical Care Survey (NAMCS); e National Health and Nutrition Examination Survey (NHANES III). Para maiores informações, vide GOLDMAN; SMITH, 2005

show statically significant effect of educational level on the adoption of new anti hypertension drugs.

Network effects of information (b)

According to Papageorgiu et al (2007) the diffusion of medical technologies can happen through two different channels: (a) imports of medical products (like drugs, vaccine, and equipment); (b) direct flow of medical knowledge from a few frontier countries to the rest of the world that can be easily made through information networks created by medical students from the rest of the world that study in frontier countries. The authors tried to empirically investigate whether medical technologies diffusion, by imports or by ideas transfer, helps improving the health condition in countries that import those technologies. In this case, the inflow takes place in the frontier countries to the rest of the world. From an econometric modeling by cross-section analysis, with data from 63 importing countries, mainly from OECD, the authors have shown that medical technologies diffusion relevantly contributes to the improvement of the health conditions of these countries (especially concerning life span and mortality rate). In other words, the health conditions of the hosting countries of medical knowledge and technologies – grouped under the "category" rest of the world – improved due to medical technologies imports (including medicaments and vaccine), as well as due to the development of information networks and R&D investment in the frontier countries.

This hypothesis was checked using a statics model to define the relevance of the import of medical products and the flow of medical students to countries leaders in the use of high technology to changes on average life expectation and infant mortality. The authors stratified the two types of medical import: The first was capital and equipment and the second group included medical drugs and pharmaceutics products. The estimations were controlled by *per capita* income, calories intake, number of physicians, female illiteracy rates, access to clean water and sanitation avoiding endogenous associations among variables to isolate the effect of *per capita income*. Two other variables were studied to explore the process of diffusion of new medical products. The first relates to measure of innovation of a group of countries in the frontier of medical technology and the spillover effect to other countries in the sample. The investigator proceeded weighting the countries investments in R&D in relation to the distance to those that are importers of technologies. The underline hypothesis states that the proximity to innovative countries promotes the diffusion of medical technologies. The other variable refers to the network of information and knowledge transfer established by the flow of health

student for professional training and higher education courses overseas. The data collected are number graduate students per thousand inhabitants by nationality living in research frontier countries. The data sets are for Canada. USA, Germany and UK and the data source are Institutes and statics Department related to teaching. In this study the variables that presented higher elasticity on health indicator were import of capital and medical equipment.

The authors refers to a debate on the increase in health indicators and income, arguing about this relationship to the evolution of country *per capita income* or if there are relevant external causes (non-income).Support of the external causes argument comes from the evidence that medical technologies embodied in medical exports or in the transfer of ideas and information, independent of income, contribute to health status of the recipient country. Thus, the variable that measures the import of medical product may convey the impact of new medical technologies on the overall health indicators of the import countries. The transfer of information may allow the health professionals to have a more effective health practice using the the knowledge and ideas from border countries.

Berndt et al (2003) have argued that externalities arise when the use of a drug by others affects its value and/or transfers information on the efficacy and security to patients and physicians. Externalities could, therefore, affect the market diffusion rate of a new drug, as well as lead to the dominance of a certain drug, even when close substitutes are available. Those authors have analyzed the role of the "consumption externalities" (called by them network effects, in BERNDT et al, 1999) in the demand for innovating pharmaceutical products (in this case, anti-ulcer drugs), in relation to both the trademark and the therapeutic class. Making use of data from a particular therapeutic class - H_2-antagonist antiulcer drugs (Tagamet, Zantac, Pepcid e Axid) - , they estimated a dynamic simulating demand model and quantified the effects of the consumption externalities from 1977 to 1993. The elaborated model has three components (a) hedonic price equation – that measures how much the aggregated use of a drug affects the trademark valuation - , (b) equations that relate equilibrium market shares for quality-adjusted prices to levels of commercialization, and (c) diffusion equations that describe the dynamic adjustment processes. The data referred to the North American market and came from IMS America.

As result, Berndt et al (2003) observed that consumption externalities influence the evaluations and new drugs diffusion rates, however they operate only at the specific

trademark level (not at the therapeutic class). Therefore, at trademark level, they remarked that past sales both contribute to the trademark value (only a small percentage) and have a significant economic effect on the diffusion rates. Such results, according to the authors, have important strategic implications. It is suggested that in terms of consumer's evaluation, the pioneer firms enjoy benefits for being the first ones to market the new drug and to establish a big base installed before the entrance of a new company. However, in the case of anti-ulcer drugs, the consumption externalities were not big enough to prevent a second entrant from surpassing the pioneer trademark.

Health insurance-plan characteristics (c)

According to Cutler and MacClellan (1996), three factors have more strongly influenced the diffusion of angioplasty to treat heart diseases, which are: the kind of refund from health insurance, the technology regulation, and the interaction with the health service suppliers. The authors have elaborated a data sample from the Medicare demands from old age patients that were hospitalized due to acute myocardial stroke in more than 3.000 hospitals in the USA, between 1984 and 1991. The work has contributed to understand the diffusion of angioplasty through two channels: the number of patients that were submitted to treatment and the hospitals decision to acquire and make the technology available. This was a work of microeconomic dimension, whose results pointed out to the importance of the regulatory environment on new medical technologies diffusion, showing variables capable of affecting the decision making of the economic agents. In particular, it is noticed that health insurance generosity affects the angioplasty diffusion. In other words, when the earnings from the medical procedure are higher than its marginal cost, technology diffusion tends to take place.

Another work of microeconomic dimension studies the consequences of a specific modality of health plan. Crown et al (2004) have investigated whether the co-payment from the non-insured patients and the physician's prescription, influence the treatment adopted to asthma patients. They have evaluated the relationship between medication consumption and the controller-to-reliever ratio. The data came from MarketScan, a private database available for the years between 1995 and 2000. The authors concluded that there were no significant negative effects on the increase of co-payments from patients on the kind of treatment followed. However, medical preferences influence the patient's treatment.

Severity of patient disease (d)

Vakratsas and Kolsarici (2008) distinguish two specific kinds of market for new drugs, "early" and "late" adoption markets that keep a close relation with the severity of the patient's disease. The first one would include patients with serious health problems, which would create previous demand for a new drug. This would happen even before its entrance on the market. The second one would concern patients with minor health problems, whose market would be created only after the launching of the new medicament. Cong (2009) elaborated an empirical study focused on the relationship between the severity of the patients' disease and drugs diffusion. By making use of a microeconomic model, he tried to analyze the diffusion patterns of a new drug among the different sub-groups of patients along a period of time. Atorvastatin, as object case study, was the innovative drug recommended for treatment and prevention of heart diseases. Data on clinical effects of atorvastatin by patient sub-groups were obtained from the systematic review of the clinical literature (especially in Oregon Health & Science University - OHSU Report). Data relative to this drug use were obtained through the Medical Expenditure Panel Survey (MEPS) in the United States for period 1996-2005. The results demonstrated that high-risk-patient sub-groups presented higher probability of adopting a new drug like atorvastatin. However, such relation tended to decrease in low-risk- patient sub-groups .

On the other hand, Valenstei et al (2006) evaluated through generalized estimation equations, the influence of the patient's characteristics on the adoption of a new drug, specifically the anti-psychotic ziprasidone among schizophrenic patients of the Department of Veterans Affairs (VA). Data (on the demographic characteristics, diagnosis, and ambulatory pharmacy) were also obtained at VA, through the National Psychosis Registry. The sample included patients that were diagnosed as schizophrenic and have received oral anti-psychotic medication between 2001 and 2003. The results demonstrated that the patients who had had previous psychiatric admission or diabetes were more receptive to ziprasidone. In conclusion, the authors remarked that the use of such drug expanded rapidly among schizophrenic patients after the approval by the US Food and Drugs Administration (FDA), suggesting that both patients and physicians were bound to experimenting new anti-psychotic drugs. In summary, the results suggested that early adoption was associated with clinical factors, like diabetes, and non-clinical factors, like race, gender or ethnics

Clinical practice (physician prescription) (e)

The specialized literature points out that the physician's prescription plays an important role on new drugs diffusion. This happens at least in developed countries, where, in thesis, the regulation on medicament sales is more effective (FOOTE; ETHEREDGE, 2000; JOHANNESSON; LUNDIN, 2002). According to Vakratsas e Kolsarici (2008), the physician's prescription is a component that has growing importance to patient care and is also a critical factor for health economics. In their study, the authors proposed a dual-market model on the diffusion of new medicaments prescriptions. This was based on clinical handling and pharmaco-epidemiology concepts, which, according to the authors, permit considering the severity of the health problems. Such model distinguished between "early" and "late" market adoption. In the first case, patients with severe health problems were considered the ones whose demand is accumulated even before the new drug launching. In the second case, drug prescription for light health problems was considered. It has been admitted that as market is expanded later, it is potentially developed by launching new drugs. Monthly data on the number of new prescriptions were used, as well as marketing mix information for a recently developed therapeutic class. In respect to the confidentially of the information source, data relative to the therapeutic class and to the market in which the new drug was launched were omitted by the authors, since they were supplied by a company that competes in the American marketplace. Data relative to marketing information mix include the IMS Health data on advertising, dollar expenditures in physician's journals; detailing effort (expressed as the number of details for the specific product); sample pack volume; and A.C. Nielsen-audited data on direct-to consumer advertising dollars. The set of data covers a period of 85 months between April 1999 and May 2006. According to the authors, the results suggested the pertinence of the model for analyzing the diffusion of new drugs (giving emphasis to the disconnection between early and late adoption markets), as well as in relation to its predictive character.

The model[3] advanced by Vakratsas e Kolsarici (2008) is based on three hypothesis: the existence of two independent markets, i.e. the adoption process of a new technology in one market does not influences the adoption of the same technology in the other; The medical

[3] The model estimates Nt $N_t \begin{cases} M_1[F_1(t)-F_1(t-1)]+\varepsilon_t, \text{with prob} \quad \pi_t \\ M_2[F_2(t)-F_2(t-1)]+\varepsilon_t, \text{with prob} \quad 1-\pi_t \end{cases}$ where N is the number of prescription t is time the subscript 1 and 2 refers to early and late market. *F* is the cumulative distribution function for adotion times, F_1 is a n exponencial function and F_2 follow a generalized Bass Mod$_{el}$é uma função exponencial e F_2 segue o Generalized Bass Model (ver Bass et al, 1994) and is dependent of the market mix variable.

prescriptions on the early market precedes those of the late market; the two markets have different potentiality. Therein, the prescription diffusion process take on a pattern where the early market hidden demand is accomplished as soon as a new drug arrives to the market, since the patients present a clinical condition more advanced and a well established diagnosis. In this case the prescription diffusion is high in the beginning and decreases with time following an exponential path. Next the prescription process starts on the early market as the diagnosis become more reliable and the ("watchful waiting") period is over. According to the authors, in this market the diffusion will follow the pattern of the Bass et al (1994)[4] model. The results suggest that the early markets not influenced by the sales effort. However the market mix variables contribute to explain the diffusion behavior on the late market. Thus, as it happens to other products the medical drugs can create market from sales effort.

On the other hand, Steffensen et al (1999) have analyzed whether the concept of early or late adopter is universal to new drugs diffusion, as well as whether it is associated to non-scientific factors, within the general clinical practice (or physician's prescription). The authors have used a population database coming from the 'Pharmaco-epidemiologic Prescription Database of County of North Jutland, Denmark' (490,000 inhabitants) to identify all the prescriptions for five new drugs (sumatriptan, finasteride, tramadol, clarithromycin and azithromycin), between January 1st 1993 and December 31st 1996. A logistic regression was used to forecast the prescription, based on the physician's attributes, the practical activity and the number of prescriptions, adjusted by age and gender. Among the main results, it was observed that the shape and the slope of the diffusion curve showed high dependence on drugs. The predictive value of the three adopters (early, intermediate and late prescribers) was low among the five drugs, even among drugs of the same family. The most consistent condition was the late prescriber condition. The late prescription of tramadol, for instance, compared to the intermediary prescription, was associated with female physicians, shorter lists, a strong restrictive attitude towards pharmaceutical-therapy, and a tendency to a lower diagnosis activity per patient. Steffensen et al (1999) propose that strategies to change the physician's behavior frequently have focus on high prescribers when they should target the late prescribers. According to the authors, taking such a change becomes a challenge to health professionals and to policy makers, if the objective is the rapid diffusion of new drugs in the population.

Intellectual property rights (f)

As it is known, the weak protection of intellectual property rights is a remarkable characteristic of the developing countries. Among the consequences of such fact, it can be mentioned the low stimulus to launching new drugs and to accomplishing R&D focused on the epidemiologic necessities in these countries. Among the reasons for the lack of an effective system for protecting patents, lies the free-rider behavior, as well as the temporal non-consistence of the intellectual property rights protection. Usually such behavior is not expected in developed countries because their governments, alleged to be more stable, would be more bound to invest in the conception of a good reputation at long term. (KREMER, 2002).

Lanjouw (1998) studied the implications of patents introduction in India, in terms of social welfare, measured by the consumer and producer's surplus and by new drugs diffusion. To the author, while theoretically those impacts can be ambiguous by creating incentives either to accelerate or to retard it, apparently in practice the patents are not decisive. The reasons that make the launching of an innovation difficult in India can be a matter of administration, as the fulfillment of the local authorities' requirements to obtain the sales authorization, or the patent holders' hesitation when making clear the price differentials charged in other markets. However, as time goes by, there is a tendency of the companies to launch their innovations in the developing countries market. Lanjouw (1998) speculates that in the developed economies the attention of the regulators on a new drug is stronger over the first years of launching. In this way, the price differentials become less important, with time. Nevertheless, among the medicines considered essential by the World Health Organization, only a minimum share is subject to patenting, which reinforces the thesis that the price differentiation strategy is the determining factor to the decision and to the period of time for launching new products in developing countries (ATTARAN, 2004).

Lanjouw (1998) tried to distinguish patents static and dynamic effects, by presenting possible results when the analysis takes place in a sole country, or when the analysis is made within a multi-country situation. Under the consumer's view, the static effect, considering only India, would be a loss of well being expressed by the monopoly power granted to labs, and the resulting price discrimination. Nevertheless, this effect is only a matter of income transfer. To the economy as a whole, the loss would be the sum of the deadweight loss typical of a monopoly and of the administration costs of a patent system. This loss is offset by the

dynamic benefits that in thesis the patents create, such as the stimulus to investment in research and development and the positive externalities to the pharmaceutical industry, resulting from information flow.

Within a various countries context, the discussion must be qualified. Lanjouw (1998) argues that if the patent holder granted by a certain country is a foreigner, the income transfer from the consumers to the producer implies a net loss to the local economy. This happens for instance through royalty payments or through profit transfers abroad. The lack of such system in India has permitted the emergency of an industry capable of rapidly copying trademarked medicaments. Therefore, if a patent is introduced, its holders will have the additional benefit of not facing anymore India generic medicaments competition in their global sales. In this case, the local labs lose the advantage of the first-mover. There are also important qualifications on the dynamic effects when more than a country is considered. Within this context, the incentive to investment in P&D created by patents in developing countries will be merely incremental. The price discriminating strategy may be a sufficient reason for delaying the launching of a new drug in a longer period than the time necessary for a local lab to imitate the trademark product. In this way, the introduction of patents would be in fact retarding the product availability to consumers in developing countries.

Lanjouw (1998) worked on interviews with key-actors, including executives of the Indian industry and of multinational companies, members of institutional organizations, such as the Organization of Pharmaceutical Producers of India, or the Indian Drugs Manufacturers Association, as well as scientists, health professionals, and government authorities. Concerning the process of new drug diffusion, two aspects were evaluated. The first one deals with the argument that the patents have contributed to the diffusion of scientific information. Consequently the Indian firms could save money by avoiding the replication of a research effort. Nevertheless, as argued by the author, since most of the innovations are internationally patented, their specifications are available to the Indian firms through computerized database, therefore the referred benefit would be redundant and merely marginal. The second aspect is related to the patent introducing impacts on the speed diffusion of new medicaments. While, in thesis, those impacts can be ambiguous by creating either incentives to accelerate or to retard the diffusion, in practice, apparently the patents are not a decisive factor. As the author found out, the reasons that make the launching of an innovation in the Indian market difficult could be of managerial order, especially the fulfillment of the local authorities' requirements

to obtain sales authorization, or the patent holders' hesitation when making clear the price differentials charged in other markets. However, the companies would tend to launch their innovations in developing countries as time went by. Finally Lanjouw (1998) speculates that the regulators' attention on a new drug is higher in the first year of its launching in a market, in a way that the price differentials would be less important as the years passed.

On the other hand, Borrel (2003) presented empirical evidence from econometric models whose results seemed to reinforce Lanjouw (1998)'s findings. The author evaluated the patents impact on the dynamics of new drugs introduction in developing countries, specifically the case of anti-retrovirus. He contributed to identifying the determinants of new medicines availability in these markets. Borrel (2003) has worked on model of discrete choice that assumes a medicament will only be marketed if the net expected value of its sales before its market introduction is greater than zero. In other words, the net benefits updated to the present value were greater than the fixed costs for inducing a new medicament. The estimations were made according to a Probit model in which the independent variable pointed out the medicament availability in the country. The construction of the explicative variable patentability has permitted the inference of the patent impact on the supply of medicaments. Such variable indicated whether the lab that developed the original version of each medicament could obtain exclusivity on its commercialization for a period of time in a certain country or not. The medical drugs can be subject of getting a patent, if the acknowledgement of the originality of its therapeutic substance comes after the date on which the cession of patents was required, either signed at the World Trade Organization (WTO)[4] or acknowledged by the international legislation. Since elaborated in such way, this indicator is exogenous to the actions of the governments and firms. It doesn't reveal the current status of the patent either, but it shows the patentability regime to which it is subject. In order to contemplate the medicaments heterogeneity (dosage, adverse reactions and its time in the American market) control variables were introduced. The heterogeneity among countries was controlled by a regression through two variables, per capita income and Gini index (for inequality).

The work has made use of 15 anti-retrovirus drugs[5]. The data correspond to a sample of 34 countries of low and average income, divided into 21 countries and two more regions that

[4] The so called TRIPS, or Agreement on Trade-Related Aspects of Intellectual Property Right.
[5] Zidovudine (AZT), Didadosine (DDI), Zalcitabine (DDC), Stavudine (D4T), amivudine (3TC), Saquinavir, Indinavir, Neviparine, Ritonavir, Delavirdine, Lamivudine-Zidovudine, Nelfinavir, Abacavir, Efavirenz, Amprenavir.

contemplate the other 13 countries[6]. The evaluated period correspond to the years between 1995 and 1999. The data of annual sales to the analyzed period were obtained at IMS Health. The found results suggest that the probability of a medicament being available in a low or average-income market varies directly with the time this drug has been in the North American market. Countries *per capita* income and medicaments efficacy also increase the chance of its commercialization. On the other hand, adverse effects or dosage growth, have negative signal on the regression. Concerning patentability, the findings show that during the first year, the probability of a medical drug being available increases where there is no patent protection. However, for two or four years since a new medicament has been introduced in the North American market, depending on the functional shape of the estimated regression, the patents boost its commercialization in the developing countries. Borrel (2003) concludes that the international labs adopt a strategic behavior that values the price differentials among markets. In this case, the incentive coming from patents is not sufficient to assure the marketing of new medicaments in the developing countries over the first years of the drug launching. The author speculates that this can happen due to the redundancy of the patents in relation to the typical advantages of the innovator over the initial life period of a product. However, to the author, the main result of his empirical study is that the patents significantly increment medicaments availability in low and average income countries.

Yet Archila et al (2005) have discussed the influence of the intellectual property laws on the Colombian pharmaceutical sector. The authors analyze information relative to the cost of the most relevant illnesses treatment under Colombia public health perspective. The database made available – individual registrations of health service provision (RIPs) – was obtained from the Health Protection Ministry of that country and contained information on the hospital and ambulatory expenses according to the Disease International Statistical Classification and Problems Related to Health. The authors identified alternative therapies to selected pathologies and the active principles of the medicine recommended to medical treatment[7], to start evaluating the patent regime of the referred medicaments. It was also elaborated an econometric model to identifying the variables that explain the price structure of the medicaments, including indicators related to intellectual property rights. The entrance of new

[6] África Francófona Occidental (Benin, Camerún, República Democrática del Congo, Costa de Marfil, Gabón, Guinea y Senegal), América Central (Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua y Panamá), Argentina, Bangla Desh, Brasil, Chile, Colombia, Ecuador, Egipto, Filipinas, India, Indonesia, Malasia, Marruecos, México, Pakistán, Perú, República Dominicana, Sudáfrica, Tailandia, Túnez, Uruguay y Venezuela.

[7] According to the United Nations' list of essential medicaments, to medical literature, inquiries to specialists and validation by the scientific community

active principles in the Colombian market was discussed and compared to the entrance of new active principles in the North American Market, according to the new medicaments sanitary registration at the INVIMA (National Institute of Food and Drug Surveillance), of the Colombian Social Protection Ministry and at the *Food and Drugs Administration* FDA/USA. In summary, the authors conclude that the patent regime doesn't decisively influence the price structure or the cost of medical treatment in Colombia. Nevertheless, the entrance rate of new active principles focused on selected pathologies is greater in the local market than in the international market (in the USA).

Regulatory environment (g)

Atun e Gurol-Urganci (2007) stated that there is a shortage of literature regarding the knowledge on how regulatory policies and health system interact to collectively influence the adoption and diffusion of innovating drugs. In summary, the authors, based on the empirical literature review, argued that strong regulation can be hazardous to innovation access, can reduce the firms' incentive to research that focus on the development of innovating products, and can lead to well-being losses in the short and long run. However, they admit that such studies, based as they are in aggregated measures (like prescribed medicament volume and drug expenses) didn't analyze the possible impacts on total health expenses. Besides, since they are exclusively focused on efficiency (basically cost reduction), they do not adequately explore the impact of regulation on other health system goals and objectives, like e.g. user's satisfaction and patient's choice. In summary, Atun e Gurol-Urganci (2007) recognize that the literature focused on the investigation on how regulatory environment and health system changes, influence the adoption and diffusion of new drugs is very limited in scope. Therefore, reflecting a partial understanding of the innovative process of the bio-pharmaceutical sector and consequently the complexity involved in translating new knowledge in new drugs (in other words, innovation).

On the other hand, Lanjouw (2005) analyzes whether the country regulatory policies influence the entrance of new drugs in their market and how they affect the speed of this entry. The author discusses mainly the effects that price regulation and intellectual property right have on the labs decision of launching a new drug in the market. The empirical approach include a sample of 68 countries and an econometric model that seeks to identify, separately, the determinants of new drugs launching in rich countries and in low and average income

countries. The data series was obtained at IMS Health and ORG-MARG, an Indian company of market research. In summary, the results pointed out by the author indicated that both the short term protection of patents on products and the long term protection on the manufacturing processes encourage and accelerate new drug launching in low and average income countries. In rich countries, a more rigorous system of patent defense that include long term protection of pharmaceutical products stimulate the entrance of new products. The conclusion is very similar in regards to price regulation, in other words, more rigorous controls have greater effect in rich countries – no stimulus to new drugs launching. Rigorously, within the author's evaluation, price control doesn't have influence on the entrance of new drugs in both low and average income countries; however they retard the entrance speed of new drugs in these countries. Although inequality, measured by Gini index, raises the probability of new drug entrance in lower income countries, in more affluent markets the greater the population share of the middle class, the higher the probability of a new drug to be launched. In summary, although the regulatory environment is an important variable, it influences in a different way the different markets, according to their income level and market potential.

Market characteristics (h)

As it was mentioned, certain aspects distinguish the markets of developing countries and impose new challenges to the understanding of the innovation diffusion process. For instance, the small size of the pharmaceutical market in these countries compared to the market of the developed countries. The North American, Japanese, and European markets together correspond to more than 80% of the sales of the Pharmaceutical Research and Manufactures of America companies, as Latin America, Southeast Asia and China stand for 15% of the total. (KREMER, 2002). Data from World Health Organization revealed that, in the year 2006, health total *per capita* expenditure in the USA was US$ 6,700, while in Brazil this value reached only US$ 765 and in China, US$ 342.

The importance of *per capita* income on the diffusion of medical technologies was studied by Slade e Anderson (2001). These authors examined the effect of the income on new medical technologies diffusion[8] (excluding pharmaco-products and medical drugs) in OECD countries. They have elaborated a model in which the *per capita use* of the new technology is

[8] The referred technologies are: magnetic resonance imaging machines, computerized tomography scanners, kidney transplant, liver transplant, and hemodialysis treatment.

explained by the following variables: *per capita* income, percentage of the population above 65 years old, ratio of health public expenditure over the total public expenditure, number of physicians by a thousand inhabitants, an indicator of the countries that reimburse the hospitals based on the number of beds available, or based on specific services. The author in fact estimated the income elasticity of the use of technology conditional to other variables. The data were obtained by OECD surveys and cover years 1975 to 1995. The results suggest the hypothesis that the income could affect the diffusion of new medical technologies. However, the investigators point out that income influences technology availability to decrease with time. The rich countries are early adopters of new technologies but the access to it becomes less dependent to income with time. The inference is based on the comparison of income elasticity of the availability of each technology. The income has higher influence on the availability of magnetic resonance imaging machines than older computerized tomography scanners. The income elasticity decreases with time even faster after five years.

A variety of explanations were raised by Slade e Anderson (2001) for their research results. Firstly, the model does not capture the effect of regulatory restriction. For example, countries with low income the regulation may have a negative bias to the diffusion of expensive technology that could imply a overestimation of the income-elasticity on the use of new technologies. Secondly, the utilization level of Technologies may reflect demand for investments decisions taken in the past. The income – elasticity could capture other variable effects - that are absent in the model, not the ones income.

That is the case of the development of new technologies more likely to happen in affluent economies although this decision may be dependent on factors other than income. However, as time goes by these decisions become less relevant to explain the geographic variation of the availability of medical technologies. The investigation calls attention to the systematic pattern presented by income-elasticity to different technologies that could reveal inconsistency with the possible omission of variables. In relation to the financing of new technologies the authors' objective was to search for the role of incentives looking into three alternative means of reimbursement using a binary variable. In the first alternative the hospital is reimbursed by the past history of the medical and procedure costs, known as block grant reimbursement. In this case if the expectation of future payments is known and previously fixed then there are no incentives to adoption of new technologies. However, cost control would be less if the reimbursement varies with present costs. The second financing alternative is the payment

according to the number of hospital beds witch creates an incentive to bring down the cost per bed. Therefore it could reduce the incentive for investments on new technologies. The third alternative was to reimburse as a fee for service system will produce an opposite bias to increase the provision of services to charge higher reimbursement. The analysis of the results did not show conclusive finds. The control variables introduced in this study did not show a relevant contribution to predict the availability of new technology.

Desiraju et al (2004) have investigated the diffusion of new drugs in 15 developed and developing countries, comparing the relative attractiveness of the different countries in terms of their market potential. The considered variables were the maximum penetration potential and the diffusion speed of new drugs in those markets. These authors also verified the influence that the price has on the diffusion speed of a new drug, focusing on the market expansion in developing countries, which has growing interest to the industry.

Desiraju et al (2004) raised the hypothesis that the diffusion speed tends to be lower in developing countries. This is due to the fact that in these countries factors like lower income, less expenditure in health – either as GDP percentage or in terms of *per capita* income, higher percentage of the rural population, higher price demand elasticity, and other characteristics would lead to a reduction of the diffusion speed of new drugs. To test such hypothesis, the authors estimated the diffusion speed of a new product, within a cross-countries situation, through a logistic regression whose dependable variable was the growing rate of sales and the explicative variables were the cumulative sales and the population. The coefficient related to the population measures the maximum penetration potential of a product, in other words, the maximum volume of sales, in kg, linearly related to the population size. In this case, the diffusion speed is understood as the necessary time to move from a certain penetrating level to a higher level within the market. To estimate the coefficient, the authors used the Hierarchical Bayesian method, making use of the possibility of estimating specific coefficients to each country. The empirical analysis data were obtained from the owner of a medicine drug trademark. Such data are made of quarterly observations of the sales and prices of a new category of anti-depressives (Selective Serotonin Re-uptake Inhibitor – SSRI). The observations cover the period 1987 to 1993. The prices were quoted in equivalent US dollars

at basic prices; the sales were measured in kg and the *per capita* expenditure in health came from the Global Market Information Database, maintained by the Euromonitor International[9].

The main results obtained were: (i) the developing countries have lower diffusion speed and lower maximum penetrating potential, compared to the developed countries. (ii) the developed countries in which the new drug was introduced later have higher diffusion speed as the international literature had forecasted. However, developing countries having the same characteristics do not present higher diffusion speed. Besides (iii) higher health *per capita* expenditure has positive effect on the diffusion speed, while higher prices of medicaments have the opposite effect. The authors warned that the latter result was statistically significant in Brazil only. Finally (iv) the accumulated sales variable has big effect on the diffusion speed, suggesting that the previous users' database is an important factor to the process of new drugs diffusion. The authors speculate that such results are directly related to the level of economic development of the countries within the sample. For instance, the lower diffusion speed of the developing countries would be a result of a lacking infrastructure for rendering health service that can be exemplified by less availability of hospital beds and of health professionals per inhabitant, or by less *per capita* expenditure in health. The bigger rural population found in developing countries would also contribute, since this population's individuals would have less access to health infrastructure. Issues like the epidemiologic pattern or the gender and ethnic structure of the countries could also interfere in the diffusion speed of new drugs and would be themes for a future research agenda.

As limitations to the proposed studies exercises, the authors pointed out the lack of data with greater level of regional disaggregation. It is assumed that data related to more specific markets can make new inferences available. The same could happen with the data related to prescription and to medical activity. Although considering the importance of the work done by Desiraju et al (2004), it's appropriate asking whether the results are, in fact, to be generalized, especially when indicating a casual relationship between the development levels, the markets potential and the diffusion speed of new drugs. Within a sample of only fifteen countries, from which only five can be classified as developing countries (Brazil, Colombia, Mexico, South Africa, and Venezuela), the results found must be taken only as good signals of which variables infer the diffusion of new drugs. There must be made a qualification in relation to the diversity of the epidemiologic pattern of the considered countries, since the

[9] Euromonitor International is an independent information and business intelligence supplier on industries, countries and consumers (available at: http://www.euromonitor.com).

analysis is based on the introduction of only one new drug (SSRI) in these markets. Again, the results should not be generalized.

Yet Berndt et al (2007) discuss the differences among countries concerning the diffusion process of new drugs and its speed. The data on medical drug s sales were obtained from IMS Health Midas and include the sales of anti-depressive, anti-hypertensive, and anti-epilepsy medicines, classified as new class and old class, according to inquiries to specialists, physicians and PubMed publications. The authors evaluated data from fifteen countries for the period between 1992 and 2003. They investigated the empirical relation between the usage and market share of the new drugs in the market and variables like the promotional effort of the labs measured by the propaganda cost and the visiting cost of their representative to physicians' offices, or the ratio between the prices of the new drugs and of the old ones. The found results reinforce the relevance of the promotional effort, of the demographic variables and of the total expenditure in health including factors that interfere in new drugs diffusion.

CONCLUSION

The objective of this paper was to revise the available empirical evidence on the diffusion of new drugs. Special attention was given to the studies that included developing countries within their analysis. In general, such literature can be considered very scarce, in spite of the diffusion models proliferation and the abundance of applications in other diversified markets and dominium. Such fact is more evident in case of developing countries. In these ones, the evidence is limited to only two of the most commonly related factors to the diffusion of pharmaceutical novelties, intellectual property rights and pharmaceutical market characteristics. Besides those two, the most frequent factors associated to the diffusion (mentioned mainly from studies that dealt with developed countries) were: patients' socioeconomic status and education level, network effects of information, health insurance-plan characteristics, patient's disease severity, physician's prescription, and regulatory environment

The bibliographic survey covered works that investigated the diffusion both from the empirical literature focused on some specific variables and those from highly empirical nature, frequently based on diffusion models. Although mostly tied to the theoretical/empirical postulates of the neoclassic theory, the diversity of objectives and

methodological procedures did not allow the direct comparison of the different texts herein studied. Their findings are limited the particular characteristics of their study object. Therefore, they are not subject to extrapolations or generalizations to other contexts or dominium – as for the diffusion in other pharmaceutical markets, drugs, or specific therapeutic classes, although it remains a controversial issue to some authors

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