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REGULATION ISSUES ON PHARMACEUTICALS

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I – INTRODUCTION

*”Porque em minha aprendizagem ninguém me disse
o óbvio desse modo tão extraordinário.
O óbvio é a verdade mais difícil de entender.”¹
Clarice Lispector*

This paper examines recent pharmaceutical regulatory issues related to patent protection and generics in order to analyze some of the competitive impacts of the regulation. There is an increasing interest from Brazil's government about the pharmaceutical industry, particularly in the areas where regulation and antitrust matters are interrelated. This work intends, in this respect, gather information to improve the Brazilian regulatory framework, taking advantage of the US as well as the other developed countries expertise in the subject.

In Brazil, the regulation on pharmaceuticals is a responsibility of the National Health Surveillance Agency – ANVISA², an independent regulatory body linked to the Ministry of Health. The agency has the institutional purpose to foster protection of the health of the population by exercising sanitary control over production and marketing of products and services subject to sanitary surveillance (manufacturing process, and related range of inputs and technologies)³. It also has the attribution to coordinate National Sanitary Surveillance System (SNVS), to monitor drug prices and to give technical support in granting of patents by the National Institute of Industrial Property – INPI.

However, there is also a role for regulatory matters assigned to the Secretariat for Economic Monitoring of the Ministry of Finance – SEAE, which works together with the regulatory agencies such as ANVISA, seeking to identify the failures in the regulatory frame that induce a less efficient

¹ “Because in my apprenticeship there has been no one to tell me the obvious in such an extraordinary way. The obvious is the most difficult truth to discern.”

² Established by Law nº 9.782, of January 26, 1999. Information obtained at the homepage of ANVISA, <http://www.anvisa.gov.br>.

³ In addition, the agency exercises control over ports, airports and borders and also liaises with the Brazilian Ministry of Foreign Affairs and foreign institutions over matters concerning international aspects of sanitary surveillance. Other attributions are the coordination of the National Program of Blood and Blood Products and the National Program of Prevention and Control of Hospital Infections; the monitoring prices of medical devices; attributions pertaining to regulation, control and inspection of smoking products.

performance, and to promote deregulation or either rearrange the regulation design. It aims to remove the regulatory constraints to competition, whenever it is a feasible tool to grant efficiency, quality and better prices⁴.

The paper is divided into six parts, this introduction being the first one, followed by an overview of the issues involved. The third part depicts the main characteristics of the pharmaceutical industry worldwide. Advantages and disadvantages of the patent protection are focused in the fourth part. The fifth one deals with some competition issues on the pharmaceutical market, such as generics and its competitive-related impacts, co-marketing and co-payment practices. The sixth part concludes the paper, followed by the list of the bibliographic references consulted.

⁴ The Regulation Chamber of the Pharmaceutical Market (CMED), created in June 27, 2003, is composed by representatives of the Ministry of Health, Justice, Finance and Civil Staff and has the main function to regulate the pharmaceutical market and to establish criteria for defining and adjusting prices (included new presentations for drugs). The SEAE participates in the CMED as a representative of the Ministry of Finance.

II – OVERVIEW

Few industrial sectors are as sensitive to regulatory frames as the pharmaceutical one. High technology and knowledge-intensive research are the main characteristics of this industry. The world's largest pharmaceutical companies are responsible both for heavy investments in R&D and great profits in this sector, ranked as one of the most profitable in the world. Furthermore, pharmaceuticals play an important role as inputs to the health care services market and also display the same imperfections, which in turn are likely to result in excessive costs. In fact, it has been observed that expenditures on pharmaceuticals is growing at a faster rate than health care expenditures overall.

Failures observed in this market can be far more severe than those in other markets. Information problems usually arise, since the consumers don't themselves choose a medicine, but accept the advice of a doctor. They are unable to evaluate the quality either by comparison (the highly-technical product specifications makes it difficult to conclude if another drug has the same effect) or by repetition (because the maladies – and their corresponding prescriptions – may vary in frequency, and/or intensity, and/or type during an individual's life). Besides, doctors often are reluctant to prescribe medicines other than those they know and rely on.

Furthermore, pharmaceutical demand is influenced by health insurance companies because insurers can pay drug costs partly or totally – and doing so, they attenuate the individual incentives to control health expenditure, a moral hazard problem. As a result, these problems limit competition and can raise prices. Ferrandiz (2003) summarized the very important features described in the last two paragraphs as a trilogy: *“the ones who decides neither pays nor consumes, the one who pays neither decides nor consumes and the one who consumes neither decides nor pays.”*

Although the increase of the price of a commodity cannot be taken as grounds for government intervention, ubiquitous soaring costs observed worldwide in this industry provide a rationale for government regulation. In general, the primary objectives of these controls are: (i) to stimulate R&D in order to assure an innovative flow of drugs; (ii) to ensure the safety of consumers; and (iii) to control the quantity and quality of drug expenditures.

The pharmaceutical industry, more than other sectors, depends on patent protection for ensuring innovation. Research shows that several aspects of the patent process contribute to increase the costs of a drug. First of all, R&D is a costly and risky process, since only 0.01% of patented products are marketed, and few of them are commercially successful (75% of drug company profits come from 10% of all marketed drugs)⁵. On the other hand, the effective commercial life of a patent (usually 20 years for the signatory countries of the TRIPS⁶ agreement) is reduced by the process of obtaining marketing approval, thus provoking manufacturer's requests to extend the license for commercial exclusiveness.

Special agencies have been created in many countries to control pharmaceutical expenditures⁷. Controls can be made through a formulary (a list of drugs and conditions on use/prescribing that are covered by the insurance), co-payment and reimbursement policies (incentives to control that depend on

⁵ According to Glover (2002), a 1994 study of drugs introduced between 1980 and 1984 showed that, for every 10 drugs that came to market, only three covered the average development costs. It also showed that the top 20% of products with the highest revenues generated 70% of the returns.

⁶ Trade Related Aspects of Intellectual Property Rights – TRIPS, Annex 1C of the World Trade Organization (WTO) Uruguay Round Agreements, signed in Marrakech in 1994, in which the GATT member countries agreed to a comprehensive set of international rules and stronger measures at international borders to stop trade in goods that infringe on intellectual property rights. Under the TRIPS agreement, nations are obliged to rewrite national laws to make them conform to internationally agreed norms for the protection of patents, trademarks, copyrights, industrial designs, trade secrets, integrated circuits, and geographical indications. It also broadens the areas of protection to include technological areas – such as pharmaceutical products, computer software, and inventions and works arising from new technologies – that are not currently protected in many countries. (See Customs Glossary at www.asycuda.org).

⁷ In US private health care systems, this is the responsibility of private companies known as Pharmacy Benefit Managers – PBMs.

the identity of the drug/individual and sometimes establish thresholds for payments, or either encourage consumption of lower-cost generics), and regulatory constraints on physicians (guidelines for prescribing) and pharmacists/wholesalers (such as regulation of the margins/chains of pharmacies, incentives to substitution of cheaper equivalent products).

Competition law applied in the pharmaceutical industry needs the relevant market analysis based on a therapeutic classification system⁸. Since many therapeutic classes markets are extremely concentrated, the authorities are concerned with vertical and horizontal mergers/arrangements along with cases of abuse of dominance, specially those which can have negative impacts on the flow of innovation. However, it is difficult to obtain accurate market share information both because new substitute products are developed and patents expire. In addition, pharmaceutical companies often achieve agreements and joint-venture arrangements for cooperation at the research and development and/or marketing and promotion phases of manufacturing process, and these arrangements raise concerns about favoring partners and sharing information that later facilitates collusion.

Some important competitive issues of pharmaceutical markets arise with the entry of lower-cost drugs known as generics – medicines that are the bio-equivalent of previously patented ones – that usually followed the expiration of a given patent. Competitive impacts of generics are closely connected with the characteristics of a specific demand – as brand loyalty and price sensitivity – which in turn depends on the type of regulatory interventions. Although the generic entry increases competition to brand-name drugs in markets sensitive to prices, that is not the situation in those markets where prices count less than brand loyalty. In these latter, drug manufacturers can decide to launch their own brand-generics in order to keep their market power, thus requiring government attention.

⁸ This system classifies the drugs that treat the same condition in the same therapeutic class, meaning that one can be a substitute to the other.
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III – THE PHARMACEUTICAL INDUSTRY

The pharmaceutical industry⁹ operates in a worldwide market place, facing changes both in economic scenarios and in health care patterns, a high-level reliance on scientific-technological research and a long-time cycle for medicine development – which consequently leads to a costly R&D process¹⁰. In fact, there is a trade-off between scientific innovation and economics constraints that underlie the main issues related to the pharmaceutical production chain. Pharmaceutical R&D has reached its third generation with the current improvements in the area of genetics science, following the previous developments in chemistry and pharmacology streams. Nowadays the integrated pharmaceutical companies follow the stages of research, development, registration, manufacturing and sales & marketing. Huge research investments involve pharmaceutical companies, genomic companies and academic groups in alliances, joint ventures or partnerships.

Expenditures on pharmaceuticals account for between 10% and 20% of total expenditures on health care in most OECD countries¹¹. During the 1990s, these expenditures rose faster than both the inflation rates and the health care expenditure rates¹² – no matter if the responsibility is of state-owned health insurers or of private companies. This pattern has focused public policies on mechanisms for controlling pharmaceutical expenditures. Although there is a relationship between high per-capita pharmaceutical consumption and high per-capita income, it is observed that the latter alone cannot explain the former in some countries, such as France, USA and Japan.

⁹ Unless mentioned, information on this topic comes from OECD Series (2001).

¹⁰ On average, economists estimate that it takes 10-15 years to develop a new drug on an average cost estimated to be U\$802 million (see Glover (2002)). According to USA, a CBO study (1998:14), it takes 11 to 12 years and costs about \$200 million per successful product (in 1990 dollars).

¹¹ In Europe, pharmaceutical spending accounts for only 15% of total health expenditure in 2001. According to *The Pharmaceutical Industry in Figures 2004 Edition*, available at http://www.efpia.org/6_publ/infigure2004b.pdf.

¹² OECD data shows that the overall healthcare expenditures as a percentage of GNP increased from 4% in the 1960s to more than 8% in the 1990s.

In Brazil, pharmaceuticals are the principal component of health expenditures (50% to 75% of the total health expenditures) of the low-income families (1% to 4% of family income)¹³. The nature of health expenditures is regressive: generally, the 10% poorer spend a percentage of the income about 8 times greater than those spent by the 10% richer¹⁴. Expenditures on pharmaceuticals increase with the increasing in the families' income, but at a lower rate than the latter does¹⁵. The explanation of this difference seems to be based on the decision to spend rather than in the spent amount itself. This observed inelasticity in the expenditures is a reason of concern given the lack of access of the low-income families to private health insurance. The ill treatment of the poorer population is mainly done by public ambulatories and public health units.

The production of pharmaceuticals is divided into two classes according the level of R&D investments: *global firms* that perform most of the R&D, and consequently dominate the patent-protected drug market (OECD's bulk of production is concentrated in the US, Japan, France, Germany, Italy and the UK)¹⁶, and *small firms* producing for local/national markets (licensed medicines) or competing with off-patent generic medicines. In the second tier of firms competition is based on the conventional price, cost-efficiency and quality issues. In the first tier, however, the holding of total patents gives substantial

¹³ See Lisboa et al. (2001). Expenditure on pharmaceuticals is 0.3% of total health expenditures to the 10% richer. The author used income data from 1998. Medici (2003:8) found that in 1996 the spending on drugs and medical supplies accounted for 59% of the health expenses for families with incomes of up to two minimum wages, but only 19% of the health expenses of families with incomes over 30 minimum wages.

¹⁴ Medici (2003:11) found that between 1999 and 1996, families with incomes of two minimum wages or less increased their spending on health (as a percentage of total household spending) by 52%, while families with incomes of over 30 minimum wages increased their spending on health by only 15%.

¹⁵ According to Lisboa et al. (2001), while the average income of the 10th decil is about 40 times bigger than the income of the 1st decil, the expenditures on pharmaceuticals of the former are 5 to 10 times bigger than the ones of the latter. However, among the families that had expenditures on health care other than health insurance, the expenditures on pharmaceuticals of the 10th decil are only 1.5 bigger than those of the 1st decil.

¹⁶ According to *The Pharmaceutical Industry in Figures 2004 Edition*, the origin of the top 20 companies by worldwide sales, 2002: 10 American companies (Pfizer; Merck & Co; Johnson & Johnson; Bristol Myers Squibb; Pharmacia; Wyeth; Abbott; Eli Lilly; Schering-Plough; Amgen); 9 European companies (GlaxoSmithKline; AstraZeneca; Novartis; Aventis; Roche; Sanofi-Synthelabo; Boehringer Ingelheim; Bayer; Schering); 1 Japanese company (Takeda).

market power to the companies, which leads competition primarily to the basis of marketing and innovation, e.g., the development of new or improved drugs or substitute for patented drugs.

Few players keep the control on the global prescription drug industry, which is largely cartelized, exacerbating the problems of monopolies and high prices. Since 1994 a significant wave of mergers has occurred in the pharmaceutical industry, increasing this “cartelization” feature. In the US, from 1994-1999 several drug companies integrated vertically into Pharmacy Benefit Managers (PBMs), which are companies that, on behalf of insurers, negotiate with pharmaceutical manufacturers, pharmacists and prescribing physicians to control pharmaceutical expenditures. PBM functions are usually performed by government agencies in other countries.

The pharmaceutical industry in the USA¹⁷ is the leader in investments in R&D and produces and sells drugs under prescription by physicians (decision makers). Consumers frequently don't pay integrally the price of the drug prescribed, which cost is shared with private insurance companies. The market is highly regulated, and introduces 20 to 30 new drugs each year. Any commercialized drug must have obtained an authorization from the Food and Drug Administration (FDA), in a process that from creation to launching in the market lasts on average 12 years. There are great barriers to entry in this market: (i) the high costs either in R&D, or in marketing and promotion required to compete against the big companies; (ii) the difficulty to access the market due to pre-existed patent protection.

The Brazilian government tried to foster its pharmaceutical industry getting autonomy for its production (by encouraging technological searches on substances before enacting the new law on patent protection (Law n. 9.729/96)¹⁸. Unlike in the US, the insurance health companies in Brazil usually

¹⁷ Information obtained from Lisboa et al. (2001).

¹⁸ The autonomy plan failed and the country didn't become a member of the innovators club of the pharmaceutical industry, despite the richness of its medicinal flora, what was mainly credited to the lack of adequate patent protection enforcement.

don't pay for the medicines, leaving the cost burden to the consumers. However, the Regulation Chamber of the Pharmaceutical Market (CMED) is working on the definition of the reference prices to the purchase of the medicines that are in the Brazilian Single Health System (SUS) national formulary. The CMED is also responsible for establishing criteria to the definition and adjustment of prices of drugs.

Currently, there is no technological development planning in the area of pharmaceuticals in Brazil. The industry is almost fully deverticalized¹⁹ and the drugs are not available or affordable to a great part of the population, damaging their constitutional right to access to health²⁰. The deverticalization of the pharmaceutical industry has an adverse effect on the imports of substances²¹, allowing the practice of *transfer prices* by the multinational industries: inflated import prices rise the internal costs, thus reducing the profit and consequently its taxation, and simultaneously avoiding to pay royalties (also subjected to taxes) to the holding company. Nationalists call this tax evasion a subsidy to the technological development of the multinationals' home countries.

The world's largest pharmaceutical companies are very profitable organizations operating in a high-risk/high-reward environment, mainly because the profits from one or two best-selling new drugs can far offset the costly, lengthily and high-failure rated process of development. To bring new products into the market, companies spend heavily on promotion of their brand-name drugs, keeping a large sales force to influence physicians and other decision makers. In fact, pharmaceutical industries spend more on marketing and advertising than on research. Though recognized, profitability in pharmaceutical

¹⁹ Deverticalization is a form of outsourcing in which the vertical integration that was the focus of conglomerates in prior decades is segmented, resulting in the conglomerates' divesting many of the supply chain links that were not truly core competencies. In the *deverticalization* of production, many large firms actively engaged the new environment by retrenching to their so-called core competencies in design, marketing and assembly, electing to subcontract ("outsource") other activities to a series of smaller suppliers that now do much of the "real" manufacturing of components. See Whitford, Josh, *Developments in training and industrial policy in the Wisconsin*, Officina Emilia, 2003 at <http://www.officinaemilia.unimo.it/elaborati/whitford-industrialpolicywisconsin.pdf> (visited 13 Nov. 2004).

²⁰ See Lisboa et al. (2001),

industry is also controversial because it is often overstated due to inappropriate accounting measures of R&D and marketing investments²²; nonetheless, in 1996, a study of US industries showed that the adjusted accounting rate of return for pharmaceuticals was 13.3% compared to 10.3% average across 14 industry sectors.

Drugs that treat the same condition are referred to be in the same “*therapeutic class*”, meaning that these drugs are seen as substitutes from the perspective of health consumers, thus providing a proxy for the competition law’s concept of relevant market. Although there is a large number of both pharmaceutical producers and products, in specific markets there is very little competition for the treatment of a condition, leading a product to hold a high market share in some therapeutic classes.

An important key to understanding the pharmaceutical market is the classification of goods on the basis of how consumers can evaluate the quality aspects of products (quality attributes)²³. A *search good* is one whose quality is determined before purchase (typical examples are external physical attributes such as color, size, polish and style). An *experience good* is one whose attributes (such as taste, system functionality, performance, or productivity) consumers can access only after purchasing and using or consuming it (e.g., by trialling it). Quality of a *credence good* can be determined by consumers neither before nor after purchasing and using. Typical cases refer to environmental impact at the production or the consumption stage. In particular it applies to safety-and-health-related attributes such as the safety of an airplane, the nutritional composition of food, or the chemical formula of a drug. For drugs, quality is usually assured by a qualified professional working for an official certification agency.

²¹ Raw material, *fármacos* in Portuguese.

²² The calculation of the rate of return on assets excludes the accumulated intangible R&D and the marketing capital, overstating the true rate of return.

²³ See Lisboa et al. (2001). This categorization was developed by Nelson (1970,1974) and Darbi and Karni (1973).

Information asymmetry in the drug market has several sources²⁴. First, as drugs are credence goods, it can be a result of the unknown quality and the inexistence of a certification agency (and/or legal procedures on this issue) creates a natural entry barrier that confers comparative advantage to the earlier market brands against the potential entrants, once consumers don't trust on a new product till it have been either quality-certificated or accepted in the long run by the market. Hence, to assure the flow of information is so or more important as the existence of the information itself.

Second, being the physician the decision maker, the choice criteria are exposed to several levels of information lacking, mostly related to: (i) academic knowledge, self-experience and peer recommendations; (ii) the distinction of effectiveness and safety among brand-name drugs (that treat the same condition, defining the inter-brand competition), and between brand-name drugs and generic substitutes (intra-brand competition); (iii) the unawareness of the prices of the generic drugs (intra-brand competition). As a result, prescriptions are based on inertia or habit, as physicians tend to recommend the well-known (hence, more consumed and prescribed) drugs.

Third, in addition to the distinction of who chooses (physicians) and who consumes (consumers), there can be a difference between who pays: (i) the patient (as it happens in Brazil), the private insurance company (as in the US), or the public health system (as in Europe and Japan). This leads to a *principal-agent problem*²⁵: payers (principals) prioritize the health of the patient *and* the costs to achieve it, but physicians (agents) prioritize only the health of the patient²⁶.

²⁴ According to Lisboa et al. (2001).

²⁵ Also referred to as *agency problem*. Agency costs can arise when somebody (the principal) hires somebody else (the agent) to carry out a task and the interests of the agent conflict with the interests of the principal.

²⁶ The principal (payer) wants to maximize the expected utility of the patient (costs in order to get good health). The agent (physician) wants to maximize the health of the patient, and not necessarily the costs of the insurance plan, even because the information about prices is not easily available.

Moral hazard associated to health care means that people with insurance might take greater risks than they would do without it because they know they are protected. Moral hazard problems related to pharmaceuticals may arise when insurance plans pay for medicines, so the incentives to control pharmaceutical expenditures are attenuated. To address this problem, many countries adopted reimbursement policies (costs are reimbursed up to an annual limit²⁷ or a reference price) or co-payment policies (when consumers share the costs of the medicines²⁸).

²⁷ Such as occurs in Denmark, Sweden and Norway (see OCDE Series (2001)).

²⁸ Although in this case, according to Lisboa et al. (2001), the information asymmetries difficult the process, hence damaging the consumer. Issues related to co-payment systems are discussed in the Chapter V of this paper.

IV – PATENT PROTECTION

Corporations, and their increasing power in the global economy, are the new enemies human rights activists chose to fight against instead of the state governments that used to be their opponents. This trend has been noticed in the last World Trade Organization (WTO) roundtables and meetings and has come in four waves²⁹. The first one advocated consumer rights to safer products and was directed to car manufacturers, tobacco industries and food (substitute and genetically modified) products. The second wave reached exploration and extractive industries. The third one aimed unsafe and exploitative work practices in developing nations, particularly in textile and toy industries. Finally, the emerged 2001 wave has targeted the pharmaceutical industry, focusing the contrast lower access/higher prices to patented essential medicines in the developing world, mainly for the life-prolonging drugs, which combat and relieve the HIV/AIDS symptoms³⁰.

The major pharmaceutical companies can charge high prices because they hold long-term patent rights on medicines, which usually give them monopolistic power over the sales of a patented drug. The patent system was strengthened in 1994 by the Intellectual Property Rights (IPR) regime adopted by the *TRIPS agreement*³¹, which also stated for the developing countries transitional obligations and deadlines for the total compliance with its terms³². Patents are typically obtained by 20 years and enforced throughout the economic life of the brand-name drug, and can be not only on the active molecule as a treatment for some condition, but on formulation, on process, on

²⁹ Unless mentioned, information on this section comes from Joseph (2003). Waves targeted companies like Nestle (first), Shell (second), Nike and The Gap (third).

³⁰ According to Joseph (2003), the price of the HIV/AIDS drugs is essentially determined by the world's major pharmaceutical corporations group formed by Merck, Glaxo-SmithKline, Pfizer and Bristol Myers Squibb, colloquially known as "Big Pharma".

³¹ See note 6. In Brazil, TRIPS Agreement was ratified by the Decree n° 1.335 of 12/30/1994.

³² To the pharmaceutical industry, the most relevant articles of the TRIPS Agreement are: 8 (on public health and public interest protection), 27 (patentable subject matter), 30 (exceptions to rights conferred), 31 (on compulsory licenses), 33 (term of protection), 39 (protection of undisclosed information), 65 and 66 item 1 (transitional arrangements to developing countries), 66 item 2 and 67 (technical cooperation) and 71 (review and amendment). The legislation on the IRP subjects in Brazil is the Intellectual Property Law n° 9.729 of May 14, 1996.

shape of capsule/pill, on metabolites generated by the digestion of a pill and so on³³.

The primarily argument to defend patents is that, assumed that economy necessarily doesn't underlie on altruism, they provide a reward for those who spent time and money in a risky field as is the new drugs research and development. As all the contents of a product patent and its relevant production process must be disclosed for a patent concession, it is also said to ensure the flow of innovation through the information it disseminates for future R&D initiatives, thus avoiding stagnation.

Other arguments point that *the TRIPS Global Intellectual Property Rights Property (IPR)* regime is designed to prevent unfairness due to the sale of pirated copies in other than the western countries where these laws were born. Furthermore, pharmaceutical patents are justifiable because the R&D incentives are said to be essential to future enhancements of the human rights law once *they would accelerate the economic development and thus alleviate the poverty of countries*. They would do so by encouraging greater technology transfer, greater foreign direct investments, and greater local innovations within compliant states.

However, some *counter-arguments* can be raised on this issue. First, *the patent-holders ability to impose inflated prices restricts the access of poorer people to the drugs that they need*. Taking the HIV example, generally the drugs are unavailable and/or unaffordable for the around 90% of the HIV-positive people living in developing and low-developed countries³⁴, which also account for increasing infection rates if compared to the richer countries ones. Far from being only a humanitarian problem related to illness and death, the

³³ See Hollis (2003).

³⁴ According to Joseph (2003), mainly in South East and Pacific Asia, Latin America and Africa, the latter accounting for the worst-hit rates of infection among the adult population.

third world societies are suffering the economic and social³⁵ consequences of the HIV infection, and although it is not the only one, it has to be viewed as a reason for the bad quality of life in these countries. As access is much more important than the product itself, developing countries tend to be unwilling to compromise with patent protection restrictions, for two reasons: (i) the products would be developed anyway for the market in developed countries; and (ii) the market in developing countries is so small that it would not provide adequate incentive to develop new products³⁶.

Second, *the exploitation of patent monopolies can be responsible for the observed huge profit level of the industry.* It is not for sure that the industry can't afford to cut the R&D investments, once it is observed that the pharmaceutical companies reinvest fewer amounts in R&D – that is said to be the main reason for pledging patent protection – than in marketing, for example³⁷. Also, there seems to be an overestimation of R&D costs, as much of the investments in the basic research (the most risky phase, regarding future marketability) into a drug, and even in the later stages of clinical trials are done with public funds or at public expense in government and university laboratories, not to mention the tax deductions allowed for the pharmaceutical industry in many countries. Moreover, generic competition introduced the issue that patented medicines can be cheaper. Even if one considers that the cost of replication of the creation of a new product is smaller than the cost of the invention of it, R&D costs don't justify the huge differences observed in prices of some patented products and their generic partners, as came to light when the generic manufacturer Cipla in

³⁵ Such as losses in the adult workforce, increasing in the number of orphans, worst conditions to health treatment and so, thus contributing to greater rates of poverty and instability.

³⁶ Barton (2004) mentioned the best example of India, that developed its generic drug industry to make and market copies of drugs still on patent in wealthier countries, and thus became a major international supplier of drugs to countries where these products can be marketed legally because they have not been patented locally.

³⁷ Joseph (2003) mentioned that Big Pharma spends two to three times more on marketing than it does in R&D. Merck 2003 Annual Report (www.merck.com) shows U\$ 6,394.8 millions (Marketing and Administrative) against U\$ 3,178.1 millions (R&D). Pfizer 2003 Financial Report (www.pfizer.com) shows U\$ 15,142 millions (SI&A – sales, informational and administrative, including marketing) against U\$ 7,131 millions (R&D). GlaxoSmithKline 2003 Annual Report (www.gsk.com) shows £ 7,581 millions (SG&A – selling, general and administration) against £ 2,791 millions (R&D).

2001 offered to provide copies of anti-HIV drugs to Africa for less than 10% of the cost of the patented drugs.

Third, the type and rate of innovation that is currently occurring in the pharmaceutical industry is questionable. *Empirical evidence does not answer if patents indeed encourage or rather restrict innovation*³⁸, this latter via the threat of expensive patent litigation. About 80% of R&D expenditure (called “safe” R&D) is directed to drugs known as ‘*me-too*’ or ‘*copycat*’ drugs, which are slight variations on medicines that add little therapeutic value to existing medical treatments. It’s remarkable that patented “me-toos” don’t provide competition for the original patented drugs; conversely, the cost of patented drugs keep increasing, unlike it happens with patented goods in other industries, such as computer products for the information technology sector. Finally, R&D efforts follow a profitability criteria, given that there are being developed more drugs to high market-potential chronic conditions (like cholesterol or heart diseases) than drugs to cures and vaccines, and to lucrative but seldom life-threatening fields (like obesity, cellulite and impotence) than to third-world killers (like malaria and tuberculosis)³⁹.

³⁸ According to Drahos apud Joseph (2003).

³⁹ According to Joseph (2003), even if one could argue the weakness of IP rights in the developing countries as a reason for not to invest in these diseases, it is improbably that the big companies would invest in new drugs with a stronger IR framework, given the third-world inability to pay for them. The author mentioned that in 2002 was launched “*the Drugs for Neglected Diseases Initiative (DNDI), a non-profit, needs-driven research entity designed to develop drugs for the diseases neglected by market-driven R&D. Depending on its future success rate, the DNDI could challenge the economic orthodoxy which deems that profits and therefore patents are necessary to foster useful R&D.*”

5.1 – Generics and competition in the pharmaceutical market

In the pharmaceutical terminology, *brand-name* or *reference drug*⁴⁰ is the brand manufacturer medicine, which usually gets the patent protection. *Generic drugs* are bio-equivalent medicines to previously patented ones, which can enter the market slightly before or upon the patent expiration and are priced cheaper (between 20% and 80% of the originator drug's price⁴¹) to compete with reference drugs. *Similar* or *brand-generics* or *pseudo-generics drugs* are generic-style drugs produced by the brand manufacturer holding identical brand formulation and standards, but relabeled under a generic name and priced to compete against other generics.

The pharmaceutical market is bi-modal in the sense of evaluation of the product by the consumers (what is called a market segmentation on the demand): there is a group who values so-called "quality"⁴², which they attribute to a brand with a reputation well-established, and therefore whose demand is less sensitive⁴³ to changes in the brand price (e.g. there is a strong brand loyalty, so they can be called "*loyal*" consumers), and there is another who does not value "quality"⁴⁴ and is more sensitive to price changes⁴⁵, therefore tending to buy the cheaper drug that is available, usually the generic substitute drug (they can be called "*sensitive*" consumers).

Competition in the pharmaceutical market takes three forms: *among brand-name drugs* that are therapeutically similar, *between brand-name drugs*

⁴⁰ It is also called *innovator drug* (see USA, a CBO Study (1998).

⁴¹ According to Hollis (2003).

⁴² According to Lisboa et al. (2001), formed by physicians and patients that don't trust or don't have enough information about the efficacy of the generic drug. It is observed in the US market, but we believe it also happens in Brazil.

⁴³ In terms of price-elasticity of demand, it means a demand less elastic or more inelastic.

⁴⁴ This group in the USA is formed by hospitals and health care organizations, according to Lisboa et al. (2001). In Brazil, the Unified Health System (SUS) hospitals and pharmacies can be considered as part of this group.

⁴⁵ In terms of price-elasticity of demand, it means a demand more elastic.

and generic substitutes, and among generic versions of the same drug⁴⁶. Manufacturers of brand-name drugs compete for market share primarily through advertising and the quality of their products (including efficacy and side effects), as well as through pricing. Manufacturers of generic drugs increase their market share mainly by lowering prices.

In addition to patent protection, competition between brand-name drugs is limited by the expertise large companies have in getting approval in the brand-exclusiveness process and in marketing their product lines directly to health care professionals (physicians, wholesalers, pharmacists). The availability of financing a large sales force and the drug-approval expertise leads to many new drugs being marketed by a company that did not discover them.

The patterns of competition in pharmaceuticals appear to vary among countries. In a cross-country analysis⁴⁷, Pammolli et al. (2002) found that competition from generics is directly related to the regulation level of the countries for different reasons⁴⁸. First, regulation – almost by definition – keeps the prices of branded patented drugs lower, hence reducing the attraction of generic entry. Second, as patients, doctors and physicians have less incentive to substitute low priced drugs (generics) to original branded products, demand elasticity tends to be lower. Third, brand-manufacturers develop strategies to take advantage of regulatory regimes, such as co-marketing generics with generic suppliers or producing minor new products and negotiating comparatively higher prices.

On the other hand, in less regulated regimes, generic manufacturers are attracted by the higher prices of the high quality-innovator drugs. To prevent this competition, brand-producers strategy focuses on differentiating its product vis-à-vis generics, e.g. through advertising, thus operating market segmentation,

⁴⁶ According to USA, a CBO Study (1998).

⁴⁷ The countries analyzed were the USA, UK, Germany, France and Italy.

targeting the loyal consumers in order to keep or raise pre-entry prices upon patent expiration⁴⁹. In practice, in these countries, markets generate a sharp distinction between innovators and imitators (producers of generics).

Regarding the dynamics of price indexes⁵⁰, before and after patent expiry, the authors observed that prices, which usually are set at time of launching in regulated countries in Europe, tend to fall with age and are seldom allowed to be increased. In the US, on the contrary, producers practice some form of penetration pricing and, furthermore, after patent expiry, they are able to segment the market and charge premium prices on branded drugs.

5.1.1 - Competition impacts of generic entry

Competition from generics generally occurs after the expiration of a pioneer's patent. The entry costs are higher for the first generic manufacturer due the patent litigation (legal costs) even after the expiration of the principal patented drug, increasing proportionally to the market size of the brand drug⁵¹. These costs fall significantly for the following generic firms, which do not face the same legal requirements the first one does. However, being the first generic on the market has the advantage of being the first stock of the pharmacies, which will resist to switch to a different generic in the future.

The 1984 Waxman-Hatch Law⁵² stimulated the development of a generic pharmaceutical industry in the USA⁵³ while maintaining the incentives to invest

⁴⁸ According to Pammolli et al. (2002).

⁴⁹ The authors noticed that alternatively, some pioneer off-patent products (e.g., Pepcid, Zantac, Tagamet) become over-the-counter (OTC) drugs (medicines that are sold without the need of a doctor's prescription, also called "non-prescription drugs" or "non-prescription medicines") and are paid for out-of pocket. Competition by generics becomes substantial very soon, prices fall and market shares of the branded drug are eroded.

⁵⁰ Related to original and licensed products.

⁵¹ Hollis (2003) says that typical entry costs for the first (non-pseudo) generic are around one million dollars.

⁵² The Drug and Price Competition and Patent Term Restoration Act of 1984 – known as the Waxman-Hatch Act – streamlined the process for a generic drug to obtain approval from the FDA (by requiring only that manufacturers demonstrate "bioequivalence" to an already-approved innovator drug) and also allows the extension of the period of exclusivity for patented

in developing innovative drugs. Since then, the generics industry's share of the prescription drug market jumped from less than 20% to almost 50% in 2002⁵⁴. According to NERA (1998), in the European Union (EU), the weighted average of generics in all prescribed medicines by value was 15 % in 1996 – 1997. The data gathered by the mentioned study also showed that in other non-EU European states the weighted average share of generics by value was 30% and outside Europe, the weighted average by value for those OECD countries was 10%.

Incentives to the use of generics vary among countries. In the USA, prescriptions of generics were law-enforced in different ways. Now predominates the “allowed substitution” type, which allows the pharmacist to substitute the prescribed drug by its bio-equivalent therapeutic. In some states there is the mandatory substitution of the prescribed drug by a generic one⁵⁵.

Pammolli et al. (2002) observed in the US a positive time trend for the price of originals and a negative one for the prices of generics. Patent expiry slows down the trend towards higher prices of original products over time. Similarly, multi-source drugs tend to limit their price growth at the time of patent expiry and in each following quarter. Conversely, the prices of generics tend to fall continuously over time. Market concentration does not affect the prices of original products: presumably, patent protection confers strong exclusivity

drugs that contain a new chemical entity never before approved. Hudson apud Lisboa et al. (2001) says that the true benefit is to reduce the lag between the patent expiration and the generic entry, which is confirmed by the manufactures (see Glover (2002)).

⁵³ According to the CBO study (1998), other two factors that contributed to the expansion of generic sales: (i) most states had passed drug-product substitution laws that allowed pharmacists to dispense a generic drug even when the prescription called for a brand-name drug; (ii) some government health programs such as Medicaid, and many private health insurance plans have actively promoted such generic substitution.

⁵⁴ According to Glover (2002).

⁵⁵ According to Lisboa et al. (2001), in the US there are two methods to prevent the substitution: (i) the two-line method, a prescription which the physician chooses to check one of the two option-boxes, where it is printed “brand-name drug is necessary” and “allowed substitution”; (ii) the active substitution method, which the physician either checks the box “forbidden substitution” or writes “brand-name drug is necessary”. In Brazil the regulation of the Law of Generics (Law n^o 9.787/99) forbids the substitution of the brand drug by a similar one, allowing

power. Concentration, however, increases the prices of generics. Thus, price differential between the average price of respectively original products and generics grows over time and it is lower in highly concentrated markets. The number of producers and the market share of generics grow over time and they are not affected by market size or market growth. If anything, the share of generics appears to be lower in fast growing markets. Entry, but not markets shares, is higher when multi-source drugs can earn higher prices relatively to originals.

On the other hand, analyzing the European countries, the authors found that in France (and in Italy) both the prices of originals and generics fall over time. In both countries, this tendency weakens after patent expiry (in Italy the price of original products actually increases after patent expiry) and in relation to generic penetration. Concentration reduces prices in Italy, while it increases the price of generics in France. The number of generic producers increases over time in France, while it decreases in Italy: here, entry is stronger in large, slow-growing markets, where generics keep high relative prices as compared to originals. In these countries imitative products have tended to enter the market before patent expiry largely through co-marketing agreements, in the attempt to obtain higher prices from the regulators.

5.1.2 - Competition impacts of entry upon (about to happen) patent expiration

Generic drugs are said to create significant savings for private, corporate and public consumers⁵⁶. Whether and how generic and similar drugs increase competition has been the object of several studies around the world. The bi-modal characteristic of the market seems to produce different patterns of results related to competition. For example, after the Waxman-Hatch Law it didn't occur in the USA the expected competition between generics and brand drugs by the

the substitution by a generic drug only if it is not written "unauthorized substitution" on the prescription.

⁵⁶ According to Hollis (2003), the Canadian Drug Manufacturers Association (1997) estimates the savings in Canada are over \$1 billion.

same market. Studies such as the Frank and Salkever (1995)'s on the US market showed that competition among generics producers did lead to price reductions in these products (each additional entrant reduced the average price by between 5.6% and 7.2%), but brand-name prices increased after the generic entry (by approximately 1% for each new entrant)⁵⁷.

The econometric study of Hollis (2003) on pharmaceutical market in Canada showed that the anticipation of both larger market share for their pseudo-generic product and the higher prices for the branded product following generic entry is the reason for brand name firms to sacrifice profits by introducing pseudo-generics in advance of any independent generic entry, rather than delaying entry of the pseudo-generic by several months. He pointed up that the pseudo-generic strategic is commonly used in most countries with a well-developed generic industry, but in the USA⁵⁸, perhaps because of both the strong regulation structure and the active role of the FDA in fostering competition.

The author found out that pseudo-generics in fact cause an increasing in prices (that's why he said they "pseudo-increase" competition, about 1% increase in brand price per 10% increase in the pseudo-generic share) by capturing a large share of generic sales⁵⁹, hence reducing welfare. The brand recoups its losses and lessens competition by predation, using the early-entry of the pseudo-generics to "preying" on generic firms. As the typical pseudo-generics controls about 40% of generic sales in the first years of generic entry,

⁵⁷ According to Hollis (2003), competition among generics is described as repeated Bertrand competition, where firms are forced to meet the lowest price in the market or suffer a large discrete increase in market share.

⁵⁸ Nevertheless, there were attempts, as showed Hollis' mention on the GlaxoSmithKline news release, April 18, 2003, about a licensed version of its product Paxil to be sold under a generic label, upon the entry of the first independent generic.

⁵⁹ The author mentioned the IMS Health Data for 31 drugs in Canada. In 1999, the pseudo-generic share of the total pharmacy sales of these generic drugs was 34.6%.

brand prices increase about 4% than if there is no pseudo-generic competition⁶⁰.

5.1.3 - Competition in Brazil

The study of Lisboa et al. (2001) showed that competition in Brazil follows the same patterns previously described. The market is bi-modal, presenting “loyal” consumers that prefer to buy the brand drug and “sensitive” consumers that tend to buy the generic or cheaper one. Hence, there is a brand-price increase when the leaders are losing market to similar or generic drugs (marked less concentrated). Conversely, regarding competition between similar/generics drugs, the entry of new competitors causes a price reduction, and a greater dispersion (greater standard deviation) of the prices among themselves.

The study also demonstrated that the higher the market-share of the leader (market highly concentrated), the greater the ability of similar competitors to accompany the price of the leader (e.g, keeping a closer proportion of its price). If there is more competition (market less concentrated), the leader focus on the “loyal” consumers raising its price (becoming much higher than the similar ones), and the similar drugs compete for the “sensitive” consumers, reducing prices. However, the beneficial impact of the entry reduces as time that the similar drugs are competing in the market goes by, because the prices of the similar drugs tend to rise, getting closer to the price of the leader.

5.2 – Co-marketing

Pharmaceutical industries can enter into co-marketing and co-promotion agreements⁶¹. In a co-marketing agreement each party agrees to conduct, under different trademarks, independent sale and marketing of a defined

⁶⁰ The author says that the direct impact of pseudo-generics on generic drug prices appears to be similar in scale.

product, in a previously defined territory. In a co-promotion agreement the parties carry out the sale and marketing of a product under a single trademark, and cooperate in managing the overall process of commercialization, from the manufacture through to sale to the ultimate consumer. In some countries (such as Italy), co-promotion agreements are forbidden; where they are allowed, the terms co-marketing and co-promotion sometimes are interchangeable⁶².

The very fact that co-marketing and co-promotion express the presence of more than one player in the market with the same product, and hence, imply a co-ordination of policies that may include coordination of price policies to offer this product, raises competition concerns in the EU. The essence of co-marketing provides that all of the following conditions are met: (i) there are at least two marketing authorizations identical in all respects but the trade names, and all having a common origin as far as the registration dossier⁶³ is concerned⁶⁴; (ii) there is ownership by the originator of the dossier (or one of its affiliates) of the marketing rights (promotion and sale) in the contractual territory; (iii) there is contemporary enjoyment of similar marketing rights in the same territory by an unaffiliated company under a temporary agreement.

The mentioned conditions imply that the contemporary presence of more than one marketer of a product, each one independent (i.e. not linked by an agreement) from the originator of the dossier is not co-marketing, neither is a

⁶¹ Unless mentioned, information on this topic comes from Piria (2002).

⁶² This happens because European Community (EC) pharmaceutical legislation explicitly permits co-marketing, but not co-promotion.

⁶³ In order for a medicinal product to be evaluated either by the competent authorities of Member States or by the European Agency for the Evaluation of Medicinal Products (EMA), a company must submit a dossier, which is comprised of four parts. The first part contains administrative information and a summary of the dossier, which includes the Summary of Product Characteristics. In European jargon, this information is usually referred to as the SPC or SmPC, which forms an intrinsic and integral part of the marketing authorization. See Glossary at www.efpia.org.

⁶⁴ Piria (2002) pointed up that where a dossier of common origin is lacking, even if there is identical product composition and the product constituents have a common origin in terms of manufacturing sources, the activity is not considered to be co-marketing. However where there is a common dossier, it is irrelevant whether or not there are supply relationships or other commercial agreements between co-marketers, even if these consist of licenses under patents or know-how; the common registration dossier is of the essence.

marketing authorization generated by access to the dossier without any agreement with the originator (as, for instance, when the term of data protection has expired) is not co-marketing; nor does co-marketing generate the perpetual assignment of the marketing authorization rights.

In the Indian industry⁶⁵, in the earlier 1980s the most common co-marketing arrangement was manufacturing on loan license and marketing by small or big companies. By doing so, big companies solved their capacity problems and also produced at a lower cost. Involvement of both the companies gave a good boost to pharmaceutical industry, making many professional companies that adopted this mode of marketing products to become big⁶⁶. Today usually co-marketing agreements take the form of manufactured by one and marketed by other, which means that big and multinational⁶⁷ companies joined hand with a small company. This arrangement gives some advantages such as: (i) it gives cost advantage to marketing company; (ii) it allows the small company to run the factory and earn profit too; (iii) it helps small scale to become more quality conscious due to better technology transfer; and (iv) it helps small scale to become more professional due to closer interaction⁶⁸. The new trend in Indian's market is two or more companies joining hand to market products, such as the case of Ranbaxy and Cipla that join hands to promote "slow release Cipro" (2001).

⁶⁵ According to Srivastava (2001).

⁶⁶ According to Srivastava (2001), the risks were: (i) both the companies are equally involved. However, with more companies willing to invest has led to decline of this concept. This was further complicated by making manufacturing company equally responsible for quality; (ii) tax benefit if factory does fall in backward area. This factor played a role in flourishing of this concept of co-marketing. However, with government becoming vigilant advantage of sales tax and excise duty may not hold valid in future. Therefore, it is likely, this type of co-marketing will die its own natural death.

⁶⁷ And Mediterranean non-member companies (MNCs).

⁶⁸ But there are risks in this approach: (i) if the MNCs/big companies decide to withdraw or shift to other location, it will jeopardize entire planning of manufacturing of companies or if due to sudden change in demand pattern there is no further order, it can lead to job cuts; (ii) this arrangement helps in getting the product out of price control as it is manufactured by a small company. However, if the National Pharmaceutical Pricing Authority (NPPA) becomes active, then it will lead to chaotic condition and shift may take place. This will further dampen the opportunity for small-scale companies. It means dependency on big company's job for survival will diminish.

In the European Community (EC), questions have arisen related to the economic nature of co-marketing (and co-promotion) agreements (i.e., if they are horizontal or vertical agreements) and, moreover, whether the differentiation of trademarks creates a competitive relationship between the co-marketers, since the common origin of the product implies that, while one of them sells it directly to the wholesalers, the other buys the product from the first co-marketer before selling it (or manufacturing and then selling it). The antitrust authorities in Italy in 1999 heavily fined companies because the public price of co-marketed products were the same. The authorities considered that co-marketing was a vertical distribution agreement and the differentiation in trademarks generated a competitive relationship and so any concertation of prices was prohibited.

Despite the controversy on their economic nature, the choice of which type of agreement to use seems to be a consequence of the regulatory constraints imposed, since a study mentioned by Piria (2002)⁶⁹ found a trend to use the centralized procedure if it were more flexible in recognising the commercial context many products are developed. Restrictions related to requirements of a single trademark or labelling practices (that does not allow, for instance, the local representative logo to appear in the blue box of the outer packaging of a medicinal product) are viewed as inadequate to reflect the commercial interests of companies who have jointly developed products and intend to market them through co-marketing or co-promotion arrangements⁷⁰.

The main purpose of co-marketing agreements is the acquisition by the product originator of an additional force of penetration into the market, consisting of the promotional resources (typically the medical representatives) of the co-marketers, against a compensation leaving the co-marketer a sufficient profit margin. The co-marketer performs the promotional activity for

⁶⁹ Cameron & McKenna and Andersen Consulting, *'Evaluation of the operation of the community procedures for the authorisation of medicinal products'*, November 2000, <http://dg3.eudra.org/F2>.

⁷⁰ Of course if co-promotion is forbidden (such is in Italy), the companies necessarily organize cooperation as co-marketing.

the product that, even if characterized by a different trade name, is perfectly identical to that of the originator. Externalizing promotional costs allows gains in efficiency to both: the originator is more efficient in connection with the additional revenues, and the co-marketer allocates better the available resources. Under this view, one can say, firstly, that all other contractual relationships (such as license, supply, technology transfer) are subsidiary to co-marketing and aim at creating the legal-regulatory situation allowing the co-marketing activity, and secondly, even the enjoyment of transfers of regulatory and intellectual property rights is also subsidiary to the purpose of co-marketing, since the originator does not want to transfer permanently its rights, but entrust them with the co-marketer only for the co-marketing term.

As a consequence, co-marketing can be evaluated under competitive rules as a horizontal agreement, since it does exist a competitive relationship: co-marketing under different trade names is co-operation aiming at the joint promotion of products that belong to the originator (and not to both parties), and some of which are entrusted for the promotion and sale with the co-marketer. Irrespective of the supply or distribution arrangements, co-marketers operate to the same level of the economic cycle, i.e. the level at which the ex-factory price is formed. Piria (2002) argued that compensation of the co-marketer as a direct compensation for the service (e.g. a percentage of sales generated by the co-marketer), instead of as a margin between the purchase and resale price, is just another way of arranging the business relationship.

Price fixing, according to the EU guidelines on horizontal agreements, can generally not be justifiable unless it is indispensable to the integration of other marketing functions that will really generate substantial efficiencies (that in turn are related to the importance of the joint marketing to the overall cost structure of the product in question)⁷¹. Thus, in co-marketing agreements, the common determination of price of a product that is entrusted by the originator to

⁷¹ Joint distribution is thus more likely to generate significant efficiencies for producers of widely distributed consumer products, which are only bought by a limited number of users.

be promoted and, often necessarily as a regulatory constraint, distributed, appears to be a transparency obligation in a regulated market, where the price regulation mechanism permits the transfer to the consumer of the benefits arising from co-marketing.

A report from the European Commission in 2000⁷² confirmed that no company is now able to control and master internally all the knowledge required to discover and develop a new drug. Competitiveness of firms depends both on their ability to access and make efficient use of a network of collaborative relations and the underlying market for technology. Such co-operation may take place between companies and academic institutions, pure research organizations or new biotechnology firms as technology suppliers, as well as between companies themselves engaged in all the phases of the economic cycle (research, development, manufacturing and marketing).

According to the report, one difference between the US and European firms is that the former demonstrate the highest propensity to collaborate in the pre-clinical phase, whereas for the latter the collaboration in marketing is the most common practice. Furthermore, US firms act more frequently as licensors (originators) of new R&D projects as compared to European countries, which are typically licensees (developers)⁷³. The organization of the industry is also different: in the US there is not only a large number of big innovative technology suppliers (new biotechnology firms and universities), but also a higher supply of new technologies and an extensive vertical specialization (an industry that is specialized in the 'exploration' of new technologies and innovation opportunities and an industry that is specialized in their 'exploitation').

⁷² Gambardella A, Orsenigo L and Pammolli F, *A global competitiveness in pharmaceuticals – A European perspective*, November 2000, <http://dg3.eudra.org/F2>.

⁷³ The report showed that firms located in Italy and Sweden, have a high propensity to license-in in the latter phases of the R&D chain from the US, while UK and Swiss firms also collaborate extensively in the early stages of the R&D process.

Technology transfers are the typical agreements between technology suppliers and pharmaceutical companies⁷⁴. By fully engaging in the entire stream of the product life, down to marketing phase, co-operating companies get reward from the market in terms of revenue from sales. In such cases, as a result of their cooperative agreement the companies perform the co-promotion or the co-marketing of the product. The efficiencies generated will not simply be the avoidance of the 'cost of competition', but real savings resulting from the integration of economic activities.

5.3 – Co-payment

Co-payment systems, whereby individuals and the state (or a private health insurance company) share the cost of prescribed ambulatory medicines are used in order to incentive the individual consumers to control the drug expenditures. According to NERA (1998), six types of co-payment systems are found, often in combination, in all OECD countries. *Free medicines*, although they are not universal⁷⁵, supply the needy, the young, the old and those with chronic or life-threatening conditions. *Co-payments in full* are usually for medicines that are considered to be non-essential, but the classification of such medicines varies widely in different countries. A common way for health funds to impose 100% co-payments is to delist particular medicines or groups of medicines from reimbursement. Some delisted medicines remain prescription-only products. Others become for sale in pharmacies only; and in some cases they are added to the general sales list for purchase anywhere without prescription⁷⁶.

⁷⁴ Here, the consideration for the technology supplier is in terms of lump sum or royalties or a combination of both.

⁷⁵ According to NERA (1998), the concept of social solidarity differs markedly within the OECD. In Denmark and Sweden only diabetes warrants free medicines but other serious conditions such as cancer, haemophilia and multiple sclerosis do not. Japan appears to be the only country in which no prescribed medicines are free.

⁷⁶ According to NERA (1998), in 19 OECD countries some prescribed medicines are paid for in full. In nine EU states some prescribed medicines are paid for in full, the exceptions being Belgium, Greece, Italy, the Netherlands, Portugal and the UK. In the USA patients without insurance or who do not want reimbursement of prescription costs because the type of medicine concerned (e.g. psychotropic) pay in full.

Threshold co-payment systems sensitize patients to the cost of their medicines up to the threshold and preserve social solidarity by providing free or subsidized medicines above the threshold⁷⁷. This concept embodies social solidarity within the health-care system⁷⁸. In Sweden introducing a threshold system in 1997 produced a major increase in demand for about three months before and a major reduction after the new scheme began. The new system appears to have lowered the demand trend line but without stopping the rising trend.

The concept underlying *proportional co-payments* is that medicines for treating the most severe conditions are either free or have the highest subsidy from health funds. This concept embodies social solidarity. However, a drawback to such schemes is that, compared with threshold schemes for example, they reduce substantially the sensitivity of the patient to the cost of the medicines prescribed, and this is likely to distort choice. Their impact in stimulating rational prescribing and choice by consumers seems limited because real price differences between competing products are diminished⁷⁹.

A *fixed rate (or flat rate) co-payment* is a sum that does not vary with the cost of the medicine or the nature of the condition. From the point of view of the three parties concerned — the health funds, prescribers and patients — fixed rate(s) have the merit of being predictable. If the rates are set at a level to enable the national medicines bill to be in balance, fixed rates may also have the merit of social solidarity. However, from the point of view or economic

⁷⁷ According to OCDE (2001), since the bulk of pharmaceutical expenditures is accounted for by a small minority of consumers, some incentives for control of pharmaceutical expenditures can be retained by limiting reimbursement until annual expenditure exceeds a certain threshold (such as occurs in Denmark, Sweden and Norway).

⁷⁸ According to NERA (1998), 5 EU states have systems under which patients pay in part or full for medicines up to a threshold: Finland, Germany, Ireland, the Netherlands and Sweden and 7 other OECD countries also use the system. In the USA, the conditions for patient co-payments vary with different insurance plans.

⁷⁹ According to NERA (1998), proportional co-payments are found in 12 OECD countries. Outside Europe it is found with considerable variations in different provinces of Canada and in different health-care schemes of the USA.

welfare they are defective because the consumer has no knowledge of the cost of the medicines in question and therefore cannot make an informed choice between, for example, originals and generics. A further defect of fixed rate co-payment systems is that they may act as a perverse incentive if they encourage doctors to prescribe larger packs than necessary so that patients incur fewer flat rate charges. Increases in fixed-rate co-payments can influence consumer demand but they do not enable prescribers or consumers to make reasoned choices between originals and generic medicines. They appear economically inefficient in containing the cost of the medicines bill and enhancing consumers' utility through choice.

There are schemes of co-payment supplements to the amount reimbursed by the health fund ("*reference pricing*"). The logic of reference pricing thus defined has clear appeal to health-funds that can find no reason to pay more for a product with an identical or similar active ingredient, if compared to another one. From the doctor and consumer's point of view, reference pricing offers an element of choice, for they can decide between them whether a product priced at the reference price — and so requiring no co-payment — is satisfactory for the patient's needs. Alternatively they can decide that an original product or a reference priced product, both of which require a co-payment, has some advantage that justifies the co-payment.

In Germany since its introduction in 1989, the system has made significant and continuing savings for the sickness funds. In Denmark, the Netherlands and Sweden the evidence of significant savings being achieved by reference pricing is much less clear. It is said that reference pricing offers consumers a distorted choice between paying something and paying nothing. Despite these facts, reference price systems are attracting the attention of pharmaceutical experts in order to obtain a better understanding of its effects.

Ferrandiz (2003) studied the effects of implementing a reference price reimbursement (RP) system, and the response of pharmaceutical firms to a

change in the price regulation. A RP system classifies products into groups with similar therapeutic effects so that the reference price is the maximum reimbursement of the third-party payer to the manufacturers for all products in that group. Manufacturers are free to set prices. If prices set are higher than the reference price, it is the consumer who pays the difference. The objective of RP systems is both encouraging price competition and reducing health expenditures (mainly those of health authorities).

According to the author, a necessary condition for an efficient implementation of a RP system is a well-developed generic market, because the reference price will be set around the price of the generic drug – presumably the cheapest good available. However, the existence of such market is not a sufficient condition for an efficient implementation of such system. Aiming to reduce prices, a RP system should be implemented in markets where the high pharmaceutical public expenditure is due to high average prices rather than due to high consumption levels. Moreover, the price difference between the drugs grouped should be significant; otherwise, the potential cost-savings of implementing a RP system will be minimal.

The study used a duopoly model (i.e., one branded and one generic drug) and analyzed two scenarios observed in countries with such systems:

- (I) Comparing the situation where under co-payments, consumers pay the full price (co-payment=1) with the situation where a RP system exists (the consumer pay the difference between the drug price and the reference price), and the reference price is set below the price of both the generic and the brand drug;
- (II) Comparing the situation where under co-payments, consumers pay a percentage of the price (a fixed co-payment=x) with the situation where a RP system exists, but the reference price is set between the price of the generic and the brand drug⁸⁰. This means that if the

⁸⁰ The author said this is the way a RP system was introduced in Spain, so he called this the Spanish way.

consumer decides to buy the generic drug, (s)he pays the fixed co-payment set (co-payment= x); if the choice is the branded drug, s(he) pays the proportion x of the reference price plus the difference between its price of the branded good and the reference price.

The results of the study were the following:

- (I) Prices are higher under reference prices, as well as total costs of the system, although reference prices are welfare enhancing. The reference price set in this way acts as a subsidy for the producers and the net price paid by consumers is reduced. In short, consumers buy more, but at a cheaper price.
- (II) The reference price will reduce the prices and the pharmaceutical costs if it is set neither too high nor too low, because the reference price has opposing effects on branded and generic producers⁸¹. However, this result may be achieved at the expenses of reducing profits for the duopolists. But the optimal choice of a reference price has been left undetermined, regarding the observed differences in the IP systems already introduced in the different countries.

There is a controversy weather regarding the implementation of a RP system reduces or increase the incentives for pharmaceutical R&D, and the author also analyzed this issue. Two types of goods can arise after investing resources in R&D: *breakthrough*⁸² (very innovative and resource-spending drugs) or *me-too* drugs⁸³ (improvements of existing drugs, usually spending fewer resources). Breakthrough drugs create a new market, while me-too drugs

⁸¹ The reference price affect differently the generic drug (making its price to decrease) and the branded drug (making its price to increase). If the reference price in set too low, then the price of the generic good will be higher with the introduction of the reference price; if the reference price is set too high, then the price of the branded good will be set too high, but the generic good will be cheaper.

⁸² According to the CBO study (1998), the first brand-name drug to use a particular therapeutic mechanism – that is, to use a particular method of treating a given disease.

⁸³ According to the CBO study (1998), a brand-name drug that uses the same therapeutic mechanism as a breakthrough drug and therefore competes with it directly.

will have to compete with existing branded drugs and generics, if they exist. He examine how the incentives the firm undertaking R&D (the branded good producers) to become multi-producers (i.e, to produce a breakthrough drug, a me-too drug, or substitute the old drug by the new one) are affected by the introduction of reference prices instead of co-payments.

The results showed that when the incumbent firm produces a breakthrough drug, profits for the incumbent might be reduced if the RP system is introduced. If the firm produces a me-too drug, it will substitute the old drug by the new one whenever the potential demand for the new drug is sufficiently high. If this is not the case, the incumbent firm will prefer to have both goods in the market, sharing revenues, rather than concentrating sales on one drug (the new one)⁸⁴. He concluded that production of a breakthrough drug is more probable the lower the R&D cost of this drug with respect to the me-too and the lower the degree of market power that the incumbent firm has.

⁸⁴ The results also showed that there is no clear-cut relationship between profits earned by the incumbent firm when producing either the breakthrough or the me-too drug, irrespectively of the price regulation system.

VI – CONCLUSIONS

*”O melhor ainda não foi escrito.
O melhor está nas entrelinhas.”⁸⁵
Clarice Lispector*

The unique characteristics of the pharmaceutical industry – such as its size and profitability, high-costly and risky-based R&D investments, and dependency on innovation – are crucial to design an adequate regulatory framework that fosters competition and increasing welfare. Of course any analysis on the pharmaceutical issues must consider the differences one find when comparing the US and the European markets, the home of the biggest pharmaceutical industries in the world, and the Brazil market, whose industry does not figure among the big players. Recently the Brazilian government has brought to the agenda the debate about what would be the best regulatory frame to ensure competition in this market, given the trade-off between the needs to access medicines and the ability of the Brazilian consumers to pay for drugs.

As posed by Ferrandiz (2003), objectives of the players are different but closely linked. Consumers want better drugs at accessible prices. Health authorities want to reduce health expenditures on ethical drugs but at the same time they have to ensure that the drugs available are sufficient and efficient, while pharmaceutical firms need enough profits to ensure a constant flow of new, but more importantly, better drugs on the market.

There is room for the government action, since the pointed market failures need to be addressed. As suggested by Lisboa et al. (2001), to correct the information asymmetry related to the quality of the medicines, the government should seek to provide an adequate certification to the new drugs, including the generic ones, as well as to incentive the private producers to disclose the information about any new launched brand drug, thus increasing the level of information widespread among consumers and physicians. Information technology tools can be very useful in these matters, since the

⁸⁵ “The best has not yet been written. The best can be found by reading between the lines.”

public can directly access the information if it is available on the official homepages of the governmental agencies.

Improvements can be achieved to correct the principal agency problem by influencing the entailed agents (i.e., encouraging the use of generics by exerting persuasion on prescribers and consumers, and even on pharmacists). The authorities in nine OECD states have conducted publicity and educational campaigns in favor of generics⁸⁶. Number and cost of prescriptions can be reduced by a system of prescribing budgets on physicians⁸⁷, combined with financial penalties and rewards⁸⁸. The impact of non-financial influences, notably the provision of comparative data to overprescribing practices, is more tenuous, but it seems that all forms of influence on prescribers to contain the medicines bill — both financial and non-financial — are likely to favor the consumption of generics. Influences on pharmacists, both financial (such as discounts) and non-financial (such as regulatory obligations that compel pharmacists to offer consumers the cheapest products), to dispense generics also seem to have a significant impact on demand for generics⁸⁹.

Moral hazard problems originated by the fact that a third-part (the insurance companies) pays total or partially for the medicines are generally addressed by reimbursement and co-payment policies, since the incentives to control health expenditures are directly related with the marginal expenditure (or co-payment) that an individual consumer faces. Although this is not the case in Brazil, the discussions in the governmental level suggest that these policies are

⁸⁶ According to information obtained in the NERA study (1998). However, the same study said that no information was provided to the consultants to evaluate the effect of these campaigns.

⁸⁷ Although it may create a moral hazard that results from conflicts between the interests of prescribers, patients and health funds. Non-financial influences are less likely to create a moral hazard. A moral hazard may also occur in the case of dispensing doctors if they benefit financially from dispensing.

⁸⁸ Penalties are likely to be more immediate and profound in their impact than rewards; however, the penalties' impact on health care spending may be less than the impact on the medicines budget.

⁸⁹ The NERA study (1998) found financial and non-financial influences on pharmacists in 15 OECD countries, but no estimates of the impact were supplied.

being considered as a matter of regulation and thus it is worthy to be aware of their advantages and risks.

Co-payment policies practiced in different countries may depend on the identity of the drug, the identity of the individual or the level of the annual expenditure of that individual on drugs or on health care more generally⁹⁰. It is common for co-payments to be reduced for the poor or chronically sick, or even the medicines for these people are given free. This cannot work as a panacea, however, because free medicines clearly have no role in sensitizing consumers to the cost of medicines. By contrast, efficiency in co-payment systems can be evaluated by the degree it makes consumers to be aware to the cost of prescribed medicines; the greater the efficiency of the system, the more likely it is to engage both prescribers and consumers in discussion about what is an optimal choice of product in each individual's circumstances. Such discussion may favor generics but this is uncertain, particularly in countries where the prices of originals have been held low by government intervention⁹¹.

As showed by the study of Ferrandiz (2003), reference price reimbursement systems can lead to significant cost-savings, given that (i) there is a causality relationship between costs and prices (i.e., the pharmaceutical costs derived from the high prices instead from the level of consumption), (ii) the difference of the prices is significant, and (iii) the existence of a developed generic market. Although there is no consensus about what is the optimal level to a reference price, these schemes are in general welfare enhancing from the view of consumer, even if it may reduce profits for the both generic and branded drug producers. In Brazil, given that the low-income population is mainly attended by the public health units and ambulatories, co-payment policies must target the purchases of medicines of this type of medical unit, either by a free-

⁹⁰ According to OCDE (2001).

⁹¹ See NERA (1998).

medicine distribution or by implementing a RP system, combined or not with other co-payment schemes that embodied partial or total reimbursements⁹².

Manufacturers of generic drugs, who sell nearly identical versions of the same product, compete more intensely on the basis of price than do manufacturers of innovator drugs, who compete more on the basis of quality and other differences between products⁹³. Some key influences demonstrated by the NERA study (1998)⁹⁴ highlighted four significant drivers on generic penetration: (i) the overall level of pharmaceutical prices in a country (which accounts for 24% of the variation in generic penetration, and generally reflects the pricing and reimbursement regimes of different countries); (ii) the number of doctors having access to PC based comparative price data for medicines; (iii) generic substitution (any form) permitted in the country; and (iv) the existence of patient supplementary co-payments above a reference price. The study concludes that the overall level of medicines' prices is the principal driver, and it is also the one that embodied, in many jurisdictions, the political decision rather than the working of the market.

Regarding to co-marketing practices, whose core is promotion, some lessons can be learned from the study of Piria (2002) on the European research system. To be competitive, a R&D system needs not only to be strengthened in terms of its ability to produce more and better research, but also to exploit its innovation potential by translating this potential into economic performance. He observed that the US competitiveness in drug innovation appears to be the sum of these two effects of better in-house capabilities and more effective use of the

⁹² The study of Ferrandiz (2003) corroborated previous empirical results found by Pavcnik (2000), who studied the effects to pharmaceutical firms of implementing reference prices in Germany. She showed that producers significantly reduce prices after the reference price system was implemented, and moreover, branded producers that face more generic competition reduce prices more. As she mentioned, "*the relevant competition in the pharmaceutical market occurs between generics and the brand name version of the same active ingredient rather than across products that are therapeutic substitutes*" (Pavcnik (2000:20)). She also showed that branded and generic producers respond differently quantitative and qualitatively.

⁹³ See CBO study (1998).

⁹⁴ The study made a regression analysis that pointed the statistically significant variables with 95% confidence limits.

market for technology; European firms lag behind their US counterparts in terms of their in-house capabilities and, moreover, in the extent of their use of the market for technology. As the environment of the pharmaceutical industry has been characterized by faster changing in the last two decades, co-marketing and co-promotion practices as tools to access national markets (particularly those ones protected by regulation) will only work if they focus on innovation, that is, on co-research and co-development.

In Brazil, the small and medium size pharmaceutical companies can benefit, in terms of co-marketing arrangements, from the suggestions made for Indian's market by Srivastava (2001): in order to survive, companies can either form separate marketing company funded based on sales contribution of products, that is, marketing company formation for marketing selected products, whose costs can be shared based on product sales contribution, or they can join together to market each other products in the markets they are stronger (i.e., selling the products of others in areas where they are operating).

The peculiar pharmaceutical industry pattern of strong connections between R&D investments and innovation necessarily raises questions around the patent protection institute and its utility. While is undeniable that the TRIPS agreement has contributed to the enforcement of the intellectual property rights, which in turn are supposed to incentive innovation and the share of its benefits, it is also noticeable that the rights to property must be confronted with the rights to life and health they can threaten, given the barriers to access to essential medicines they impose to the poor people. Economic and social consequences of these barriers are most relevant to developing countries such as Brazil, once they are directly related to the quality of life, which in turn is a very important variable that accounts for the country's growth to be sustainable. As Barton (2004) pointed, it seems reasonable that the burden of the R&D costs, which benefit all of humanity, should fall more heavily on the wealthy than on the poor. The research-based pharmaceutical industry would prefer to achieve this differential pricing by a donation program or by simply charging different prices.

It is hard for developing countries to accomplish with the TRIPS conditions, for they tend to believe that access to pharmaceutical products is so much important that the products themselves should not be patented⁹⁵. Brazil and a group of African countries brought to light this controversial issue in the WTO Doha meeting (2001), leading to the Doha "*Declaration on the TRIPS Agreement and Public Health*", which affirmed the right of nations to use the exceptions of TRIPS, such as the compulsory licensing provision of the article 31 of the TRIPS agreement⁹⁶, to meet public health concerns. This originated the so-called 31(f) problem⁹⁷, which involves the manufacture of drugs under compulsory license for countries that lack the capability to manufacture the drugs themselves.

The problem gets worse when one realizes that poor countries don't have access even to off-patent medicines that are available at relatively low prices. The very fact that a country has the legal right to obtain a product does not mean that it can afford the product, particularly if large start-up costs must be covered and cannot be shared with other countries⁹⁸. Barton (2004) suggested some strategies to cover manufacturing costs. First, to work with the major pharmaceutical firms, either by requiring them to provide products at near-production cost to patients in developing countries or by purchasing products from them, at developed-world market cost and distributing them in the developing world at a subsidized price. As these price differentiation practices don't match the drug industry's economic interest, it seems essential to

⁹⁵ In fact, this was the viewpoint of India when it decided to provide low-cost drugs for its people at the expense of eliminating incentives to create new products (excluding drugs still on patent in other countries from patent protection), thus developing the Indian generic industry.

⁹⁶ TRIPS art. 31: "*where the law of a Member allows for other use of the subject matter of a patent without the authorization of the right holder, including use by the government or third parties authorized by the government*".

⁹⁷ TRIPS art. 31 (f): "*any such use shall be authorized predominantly for the supply of the domestic market of the Member authorizing such use*".

⁹⁸ The problem tends to get worse because after 2005 the Indian generic drug industry, the major supplier producer for poor regions such as the sub-Saharan Africa market, is required to change its law in order to accomplish with TRIPS agreement and may no longer manufacture the generic drugs that are still under patent.

strengthen the companies' own sense of public service combined either with specific legislation or with the threat of compulsory licensing⁹⁹.

The second strategy is to produce the products under compulsory license either in a private-sector generic industry, whose fixed costs are distributed over a fairly large market, or in a public-sector generic industry, whose fixed costs are covered by the public. The advantage of this approach is to confer to competition (as a way to lower prices) rather than to administrative price control the task of finding the appropriate price. Moreover, it might offer new opportunities for production within the developing world, what the author pointed it would be extremely popular politically with the economic leaders of these countries¹⁰⁰.

Therefore, it seems crucial to grant this access to essential medicines either assuring the right to use the compulsory licenses under the article 31 of the TRIPS agreement or providing international agreements that are based on a compromise that prices should be lower in developing than in developed countries, permitting drug firms to recover their research spending through high prices in the developed world while making products available at lower prices that are near actual production cost to the poor in developing countries¹⁰¹. Of course there must be efforts to avoid the misuse of parallel trade¹⁰² as well as the weakening of the incentives to develop products for developing countries.

⁹⁹ According to Barton (2004), the industry already supplies donations). Most likely, the international donors – probably primarily the taxpayer in the developed world – will pay a price that covers the production cost and a portion of the R&D costs of the product. For vaccines, international entities already obtain products for the developing world at enormous discounts with prices on the order of \$0.50 per immunized child.

¹⁰⁰ According to Barton (2004) having the threat of the second approach could make the first approach more possible or decrease the cost to donors. It is also possible that India – or a global entity – might choose to subsidize the fixed costs (or at least permit these costs to be covered by higher prices to Indian consumers) so that an Indian industry can export to poorer developing countries at a reasonable price. There is already a debate in Canada over ways to encourage the Canadian industry to produce generic drugs for export, and a bill has been introduced to facilitate this process.

¹⁰¹ According to Barton (2004), this approach is justified because the market in poor countries is so small that it provides only a minimal incentive. The total market of the poorest countries (for example, sub-Saharan Africa or the United Nations' Least Developed Countries) is on the order of 1 percent of the global pharmaceutical market.

¹⁰² The purchase of goods at low prices in one country and the subsequent re-sale of those goods at higher prices in another country.

Incentives to produce may be provided by public-private partnerships, which involve public or donors funds in cooperation with the private sector, even though they will have to face the problem of financing at some point¹⁰³.

Despite of all possible strategies, it remains opened the question about how to finance the special needs on pharmaceuticals for the developing world, which is part of the overall controversy that surrounds the pharmaceutical industry, underpinned by technical, economic and social factors. Although the IRP regimes may be necessary to ensure the flow of innovation and can conduct to economic growth and increasing in welfare, provided that some institutions (such as the rule of law and freedom of information) are enforced, poor people can't forgo their rights related to access essential medicines. International aid to developing countries must be administered by competent associations and corporations in order to supply the necessary medical infrastructure, in cooperation with governments. Measures to control expenditures and to increase competition, irrespective of involving co-payment policies or incentives to generic consumption, must be implemented as a counterweight to the broad monopoly effects in the industry originated by patent protection. Finally, the balance of all these issues depends mostly on political decisions, as the political agenda defines the interests to be accommodated, regarding the trade-offs between IRP protection and the resolution of potential or existent health care crisis.

¹⁰³ According to Barton (2004), patients in developing countries or the world public sector must pay for the development costs at some point, either during the research phase or later on at higher prices during the market phase. At one extreme, the public and donor sectors can support private-sector product R&D, conditioned upon charging of a reasonable or preferential price at the time the product is actually provided. At the other extreme, there have been suggestions for funds that would be big enough to guarantee a market for new products designed for developing-world needs.

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