

## **Intellectual property and pharmaceutical data exclusivity in the context of innovation and market access**

### **Executive Summary**

Data exclusivity is one of the most interesting issues in the current discussion on pharmaceutical intellectual property policy-making globally. It is aimed at protecting and safeguarding pharmaceutical registration files - the data submitted by pharmaceutical companies to regulatory authorities, such as the US Food and Drug Administration (FDA) and the European Agency for Evaluation of Medicinal Products (EMA), for the purpose of obtaining marketing approval for new drugs.

The underlying logic of data exclusivity suggests that it is an expression of trade-secrets, and that as such, data exclusivity should be independent of patents. Compared with patents, the market power of data exclusivity is, in theory, less restrictive, mainly because it does not legally prevent other companies from generating their own registration data. However, in practice, the vast financial resources and extended time required for gathering and generating pharmaceutical registration data for a new drug create a market barrier that is too high for generic-based companies.

The rising economic significance of data exclusivity is a combination of three factors: (i) the lengthy and costly process of clinical trials; (ii) the ongoing innovative productivity challenges (some would use the word crisis) the pharmaceutical industry now faces, and; (iii) the fierce legal patent disputes between research-based and generics-based pharmaceutical companies. In fact, data exclusivity is becoming increasingly dominant as an additional IP layer of protection which affects both research-based and generic-based companies.

The extent to which the term of data exclusivity extends beyond the term of patent protection is not clear, as empirical evidence is still inconclusive. Yet, it is logical to assume that, for the majority of drugs, the maximum period of data exclusivity (in the EU and the US 10 years and 5 years respectively from the day of registering the drug) is shorter than the 20-year patent term (and the possibility to extend the patent term by an additional period of up to 5 years). That said, there are three potential cases in which data exclusivity can affect the overall period of market exclusivity. The first is a situation in which the development period of a given drug is particularly long. The second case involves drugs that do not enjoy a "foolproof", or even partial, patent protection. The third and final case concerns the generic substitutes of biotechnology drugs (biogenerics).

The international distinction between patents and data exclusivity as an expression of trade secrets (or undisclosed information) is based, inter alia, on the provisions of NAFTA (art. 1711.5 and 1711.6) and of the TRIPs agreement (art. 39.3). However, the ambiguity of TRIPs with regard to the operational translation of data exclusivity at the multilateral level creates a vacuum and, subsequently, leads to the contemporary debate as to the scope and term of data exclusivity in each and every country.

Paradoxically, the ambiguity of the TRIPs agreement on the issue of data exclusivity resulted in free trade agreements (FTAs) and regional trade agreements (RTAs) that require data exclusivity legislation according to the US standards. Trade retaliation policy tools are also currently being used by the US and the EU against developing countries, such as Israel, Turkey and India, in which the absence of data exclusivity legislation results in a serious commercial clash between research-based multinational pharmaceutical companies and powerful local generic-based companies, that are often perceived as "national champions".

Finally, since data exclusivity is a new form of protection, there are still significant disagreements on what this form of IP protection encompasses. There is also a need for much more concrete empirical data in order to assess the implications (both positive and negative) of data exclusivity. A more informed empirical discussion on data exclusivity - that is also based on empirical findings - can help us to conclude what is acceptable as the prototype model of data exclusivity to be adopted at the multilateral level, including the provisions contained in Art. 39.3 of TRIPs.

## **Preface**

Data exclusivity is one of the most interesting issues in the current discussion on pharmaceutical intellectual property policy-making in the global arena.

It is aimed at protecting and safeguarding pharmaceutical registration files - the data submitted by pharmaceutical companies to regulatory authorities, such as the US Food and Drug Administration (FDA) and the European Agency for Evaluation of Medicinal Products (EMA), for the purpose of obtaining marketing approval for new drugs.

Recognized internationally for the first time in the mid 1990s, by the North Atlantic Free Trade Agreement (NAFTA - art. 1711) and the WTO agreement Trade Related Aspects of Intellectual Property Rights (TRIPs - art. 39.3), data exclusivity is a relatively new form of intellectual property.

As will be discussed later in this paper, proponents of data exclusivity consider it an integral and inseparable part of the intellectual property (IP) protection array of pharmaceutical products, while its opponents argue that data exclusivity is a monopolistic extension of the patent system.

The recent interest in data exclusivity in Europe stems mostly from the July 2003 proposals of the European Commission, titled: *A Stronger European-based Pharmaceutical Industry for the Benefit of the Patient*, and the subsequent resolution of the European Parliament, dated 17 December 2003.<sup>1</sup> These recommendations and decisions aim to strengthen the European pharmaceutical industry and to benefit patients by harmonizing the scope and terms of data exclusivity in Europe.

Data exclusivity is also rapidly becoming a global North-South issue, as it is now being fiercely advocated by multinational research-based pharmaceutical companies operating in developing countries, such as Israel, Jordan, Turkey, India and Thailand.

This paper does the following:

1. Provides a brief overview of the nature of data exclusivity;
2. Elaborates on the economic significance of data exclusivity;
3. Considers the implications of data exclusivity relating to the clash of interests between research-based and generic-based pharmaceutical companies;
4. Discusses the December 2003 resolution of the European Parliament on data exclusivity;
5. Adds some further insights on data exclusivity as a North-South issue, particularly with regard to the recent free trade agreements (FTAs) and regional trade agreements (RTAs) between developing countries and the US.

## **1. Data exclusivity as an intellectual property right**

Similarly to patents, the debate over data exclusivity is a manifestation of the ongoing 'battle' between research-based and generic-based pharmaceutical companies [*or in more general terms, between two basic social needs that constantly require balancing: (1) providing incentives for innovation, particularly in light of the costs*

*associated with the financing of medical innovations, and (2) ensuring full public access to existing medicines].*

The scope and term of data exclusivity is thus highly relevant to the public, particularly with regard to the supply of new medicines and access to existing ones. Before elaborating on the specific components of data exclusivity it is important at the outset to identify the subject matter to which data exclusivity relates.

### ***1.1 Subject matter of data exclusivity: pharmaceutical registration data***

Each new medicine has to undergo a complex and lengthy process of selection, testing and development in order to make it safe for human use and effective in terms of treatment.

A potential medicine will be constantly examined and evaluated during its development, to maximize its effectiveness and minimize any side-effects. Following initial testing, using computers, test-tube methods and testing the molecule on animals (“pre-clinical trials”), a promising compound begins three phases of clinical trials in an increasingly wide range of people, to analyse its effects on the human body and its absorption, distribution, metabolism and excretion<sup>2</sup>.

Pre-clinical research on new compounds is carried out in the company's laboratory, using a wide variety of techniques. Promising compounds are then studied in animals, to investigate effects that cannot currently be predicted from the computer and test tube studies.

Subsequently, various clinical assessments in humans are carried out following strict guidelines:

Phase I - a small number of healthy volunteers is given the compound to determine mainly that the drug is safe for human use.

Phase II - a small number of patients is given the medicine to assess its efficacy and safety and to ensure that there are no unacceptable side-effects.

Phase III: A large number of patients, usually thousands, take the medicine under supervision over a defined period of time, with the results used to establish efficacy.

If the results prove satisfactory in terms of efficacy and safety, the data gathered are presented to the medicines evaluation authorities and, after review and discussion, a marketing authorization is issued. Alternatively, as has become common, additional studies may be requested.

Following the grant of marketing authorization, the newly-authorized medicine is studied in large numbers of patients in hospitals and clinics to further assess its clinical effectiveness. This stage is called Phase IV or post-marketing study.

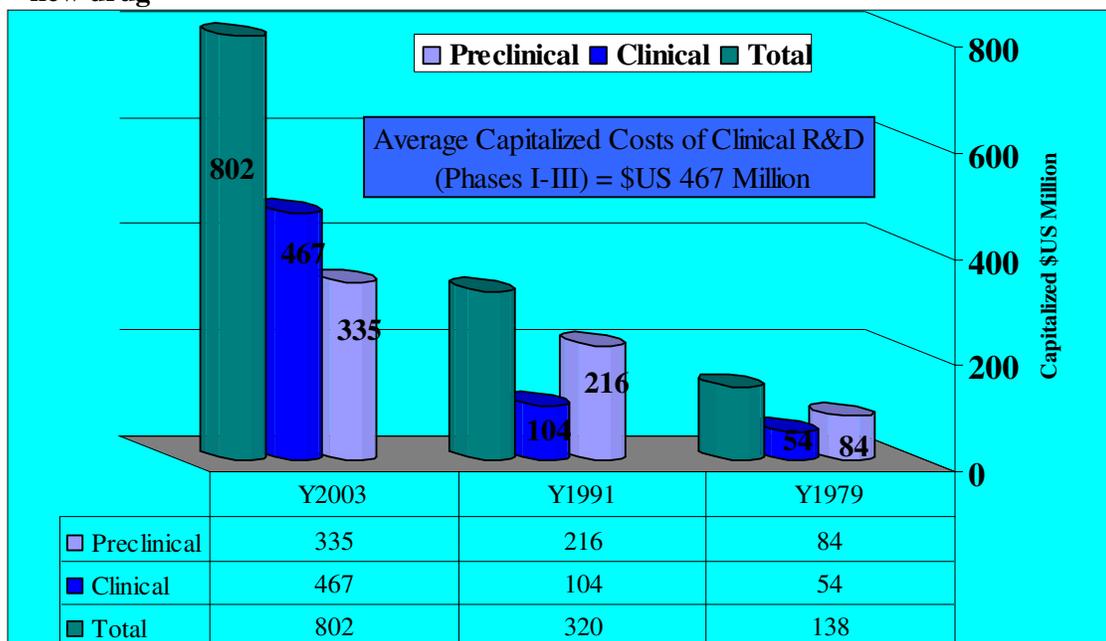
SAMM (Safety Assessment of Marketed Medicines) studies are initiated after the medicine has been made available for doctors to prescribe and to help identify any unforeseen side effects. These may involve many thousands of patients.

Physicians' databases are also used to identify medicine safety issues and to explore the potential for new or better use of medicines, once the product is available for prescription.

With regard to costs, according to Grabowski, the accumulation and compilation of the data included in a pharmaceutical registration file is estimated at \$US 467 million, more than 60 percent of the total cost of pharmaceutical R&D<sup>3</sup>. Dimasi, Hansen and Grabowski estimate the current average capitalized costs of developing a new drug are about US\$ 870 million.<sup>4</sup> Recent estimates by the Tufts Center for the Study of Drug Development suggest that the "fully capitalized cost to develop a new drug, including studies conducted after receiving regulatory approval, averages \$897 million".<sup>5</sup> Charts 1 & 2 describe the average costs associated with creating pharmaceutical registration data, based on different phases and classes of treatment.

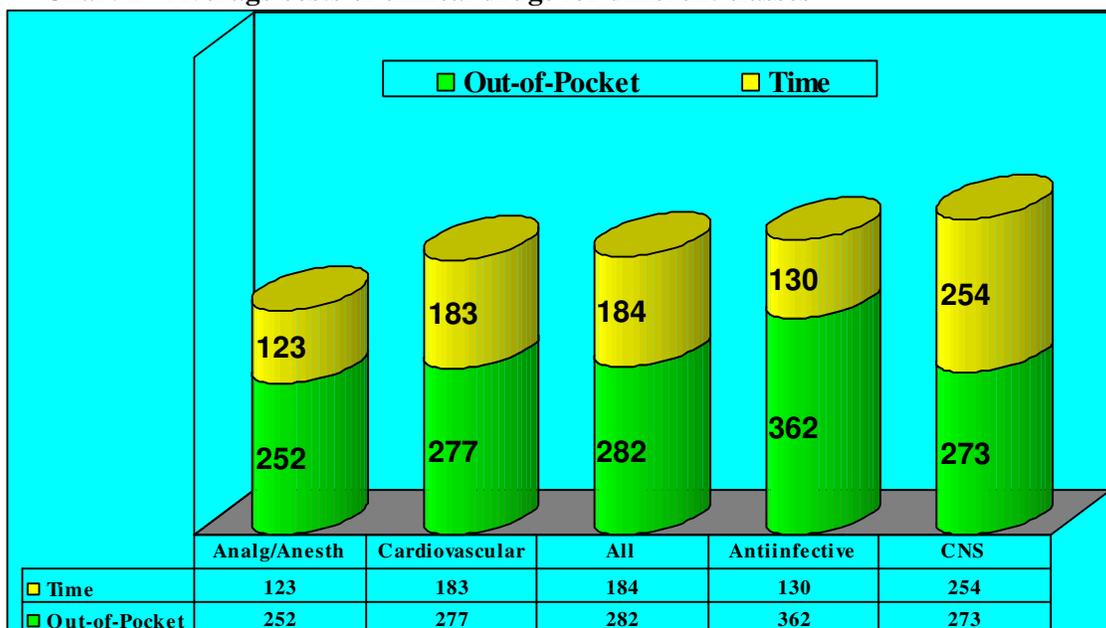
However, as indicated later in the paper (section 2) these studies have been criticized by NGOs, such as Consumer Project on Technology (CPTech), and scholars, such as Frank, as being inflated and methodologically problematic.<sup>6</sup>

**Chart 1- Trends in capitalized preclinical, clinical and total cost per approved new drug**



*Calculations based on: Dimasi, Hansen and Grabowski, October 2002; Grabowski, December 2003;*

**Chart 2 - Average costs of clinical drugs for different classes**



*Calculations based on: Dimasi, Hansen and Grabowski, October 2002; Grabowski, December 2003;*

### **1.2 Data exclusivity as an expression of trade secrets**

Theoretically, the underlying logic of data exclusivity suggests that it is an expression of trade-secrets, and that as such, data exclusivity should be independent of patents.

Why?

The patent system is based on an economic trade-off between the incentive to develop more knowledge products in the future and the grant of restrictive (exclusive) powers to knowledge owners in the present<sup>7</sup>. The term 'paradox of patents', which was coined by Robinson as early as 1956, seems to capture the true nature of this trade-off: 'by slowing down the diffusion of technical progress, patents insure that there will be more progress to diffuse'<sup>8</sup>.

Data exclusivity is based on a different type of trade-off: demanding that pharmaceutical companies provide data on the safety and efficacy of a new medicine in exchange for treating this data as a trade secret for a limited period.

Compared with patents, the market power of data exclusivity is, in theory, less restrictive, mainly because it does not legally prevent other companies from generating their own registration data.

However, in practice, the vast financial resources and extended time required for gathering and generating pharmaceutical registration data for a new drug create a market barrier that is too high for generic-based companies. Indeed, as discussed later in the paper, this barrier is at the core of the debate on the extent to which data exclusivity affects the market balance between research-based and generic-based pharmaceutical companies.

Nevertheless, patents and data exclusivity may be treated as two separate forms of intellectual property. Patents are granted to the inventions and innovations embodied in a new medicine. Data exclusivity, on the other hand, is an expression of trade secrets. It is aimed at protecting and safeguarding the proprietary know-how and information included in the registration files against any type of unfair commercial use. This leads us to the obvious question: "**what falls within the scope of unfair commercial use**"?

By definition, the data included in the registration file of a pharmaceutical product is disclosed to the health regulatory authorities. Without this data a drug cannot be approved for market use. This in turn means that the term unfair commercial use is linked to the responsibility of the Government for protecting this data.

There are two layers to this responsibility:

The first - **non-disclosure** - is quite straightforward. Non-disclosure aims to ensure that rival companies (usually generic companies) do not gain access to the registration file of the original product.

The second - **non-reliance** - is less obvious. Non-reliance aims to prevent the authorities themselves from relying on the registration file of an original in order to compare it to the chemical and toxic levels of a potential generic substitute (so-called bio-equivalence tests). The issue of non-reliance can be further complicated by the issues of direct and indirect reliance or active and passive reliance. Suffice it to say that while the US and EU take the position that any form of reliance is prohibited, some countries such as Canada, argue that the term reliance is subject to interpretation, as indicated in the 1998 court case of Bayer vs. Canada.<sup>9</sup>

The distinction between patents and data exclusivity as an expression of trade secrets (or undisclosed information) is based, inter alia, on the provisions of NAFTA and the TRIPs agreement.

Article 39.1 of TRIPs establishes that in order to prevent unfair competition, as defined in Art. 10*bis* of the Paris Convention, members shall protect undisclosed information and data submitted to governments and governmental agencies.<sup>10</sup> Pursuant to Art. 39.2, WTO members shall allow natural or legal persons to prevent information lawfully within their control from being disclosed, obtained, or used, without their consent, in a manner contrary to honest commercial practices<sup>11</sup>. In order to be protected, undisclosed information must fulfil three criteria: (1) it must be secret in the sense that it is not generally known or accessible to persons who normally deal with this kind of information (Art. 39.2*a*); (2) it must have commercial value because it is secret (Art. 39.2*b*); (3) reasonable steps were taken by the owner of that information to keep it secret (Art. 39.2*c*).<sup>12</sup>

As to pharmaceutical registration files, Art. 39.3 states that "Members, when requiring, as a condition of approving the marketing of pharmaceutical or of agricultural chemical products which utilize new chemical entities, the submission of undisclosed test or other data, the origination of which involves a **considerable effort** (style does not appear in the original text), shall protect such data against unfair commercial use. In addition, Members shall protect such data against disclosure,

except where necessary to protect the public, or unless steps are taken to ensure that the data are protected against unfair commercial use".

However, Art. 39.3 leaves three major issues unresolved. First, it does not specify the minimum period of data exclusivity required by WTO members (discussed below, the term of data exclusivity in Europe and in the US is 10 and 5 years respectively). Second, Art. 39.3 is not clear-cut when referring to the use of such information by the authorities, particularly in cases of reliance, when a member country may choose to rely on the proprietary information of the original product in order to compare it to the chemical and toxic levels of a potential generic substitute (via the so called bio-equivalence tests). Finally, it is not clear what type of activities are within the scope of "considerable efforts".

Unfortunately, the ambiguity of TRIPs with regard to the operational translation of data exclusivity at the multilateral level creates a vacuum and, subsequently, leads to the contemporary debate as to the scope and term of data exclusivity in each and every country. Although this discussion does not fall within the scope of this paper, it is nevertheless important to note that the way data exclusivity is shaped at the multilateral level (TRIPs) has some serious implications on the negotiation position of developing countries at the regional and bilateral levels. As shown later in the paper, this vacuum also allows the US to pursue a *TRIPs+* strategy with regard to data exclusivity when negotiating FTAs and RTAs. One may also think of more fundamental questions about the purpose of the TRIPs agreement in general, and more importantly, on the extent to which non-operational definitions, such as in the case of data exclusivity, benefit developing and least-developed countries. Common wisdom suggests that the weakening of TRIPs serves the interests of the developing countries. However, given the recent surge in *TRIPs+* deals at the bilateral and regional levels one may question the outcome of this strategy.

The NAFTA agreement seems to provide a more detailed prescription of data exclusivity.

Art. 1711 (5) states that when a "Party requires, as a condition for approving the marketing of pharmaceutical or agricultural chemical products that utilize new chemical entities, the submission of undisclosed test or other data necessary to determine whether the use of such products is safe and effective, the Party shall protect against disclosure of the data of persons making such submissions, where the origination of such data involves *considerable effort* (style does not appear in the original text), except where the disclosure is necessary to protect the public or unless steps are taken to ensure that the data is protected against unfair commercial use".

Art. 1711 (6) further specifies that "Each Party shall provide that for data subject to paragraph 5 that are submitted to the Party after the date of entry into force of this Agreement, no person other than the person that submitted them may, without the latter's permission, rely on such data in support of an application for product approval during a reasonable period of time after their submission. For this purpose, a reasonable period shall normally mean *not less than five years* from the date on which the Party granted approval to the person that produced the data for approval to market its product, taking account of the nature of the data and the person's efforts and expenditures in producing them"<sup>13</sup>

The two existing prototypes of data exclusivity at the national level are that of the US and the EU.

Data exclusivity **in the US** is provided by Section 355 of the Federal Food, Drug, and Cosmetic Act of 1997.<sup>14</sup> The US model provides a five-year period of data exclusivity to new drugs and three years of data exclusivity to new indications of existing drugs.

**In the EU**, data exclusivity is provided by Article 10 of Directive 2001/83/EC.<sup>15</sup> Until recently (May 2004), Article 10 stated that, for the purpose of obtaining authorization for market use, a generic drug does not require the submission of a registration file if it can be demonstrated that it is essentially similar to a medicinal product which has been authorized within the Community for a period of not less than six years. The Directive also stated that the period of exclusivity shall be extended to 10 years in the case of high-technology medicinal products and that Member states can extend the period of exclusivity to 10 years to all medicinal products.

As will be elaborated later in the paper, following a two year consultation process, the European Parliament in December 2003 harmonized and upgraded the level of data exclusivity in the EU, according to the 8+2+1 formula: 8 years data exclusivity, 2 years of marketing exclusivity and an additional year of protection for new indications of existing products.

Interestingly, both the US and European models do not fall under the category of trade secrets. Rather they are an inseparable part of the regulations concerning the approval of pharmaceutical products.

## **2. The economic significance and implications of data exclusivity**

The rising economic significance of data exclusivity is a combination of three factors:

- i. The lengthy and costly process of clinical trials;
- ii. The ongoing innovative productivity challenges (some would use the word crisis) the pharmaceutical industry now faces;
- iii. The fierce legal patent disputes between research-based and generics-based pharmaceutical companies

With regard to the **first aspect - costs** - as discussed earlier in this paper, all potentially new medicines have to demonstrate their safety and efficacy before being approved for market use. This is done through a complex and lengthy process of clinical trials which last more than 10 years on average.<sup>16</sup> Estimates, that are often quoted by research-based pharmaceutical trade associations, suggest that of every 5,000 new chemical entities (NCEs) screened, on average, only five are tested in clinical trials and only one of those is approved for patient use.<sup>17</sup> Moreover, on average, only 3 out of every 10 prescription drugs available for treatment generate revenues that equal or exceed average R&D costs.<sup>18</sup> Therefore, according to these estimates, the average \$US 870 million per-drug includes non-retrievable investments in failed molecules.

However, the above figures are sometimes criticised as being too subjective, given that they are based on figures that were provided by pharmaceutical companies with no effective ability for auditing (US office of Technology Assessment 1993)<sup>19</sup>.

Others, such as Frank, argue that calculations that are based on average costs of NCEs do not provide an accurate analysis of the true costs of pharmaceutical R&D in general, and of pharmaceutical "line extension" (new indications) in particular.<sup>20</sup> Finally, some scholars, such as Angel, argue that in many cases the costs of R&D are actually financed by the US Federal Government and its national laboratories, such as the NIH<sup>21</sup>.

Nevertheless, even if there is no academic consensus about the accurate costs of pharmaceutical R&D (be it close to a billion dollars or only to a "few" hundreds of millions of dollars), it is still clear that the process of developing and testing a new pharmaceutical product, including clinical trials, requires overwhelming financial resources and time. It is also clear that the resources required for carrying-out clinical trials in order to prove the safety and efficacy of a new drug are not available to generic-based companies, otherwise there would be no need for these companies to refer to the safety data of the original drug (bio-equivalence tests).

As to the **second factor - challenges to global pharmaceutical innovative productivity**- here we should note that the pharmaceutical industry today is in a very uncomfortable position.

On the one hand, no one doubts the long term performance and robustness of the pharmaceutical industry, which has consistently demonstrated impressive manufacturing capabilities, sales growth, innovative potential and capacity to generate profits. World production in pharmaceuticals grew from \$70 billion in 1975 to \$150 billion in 1990 and to more than \$300 billion in 2000. Sales of prescription pharmaceutical drugs worldwide grew from \$40 billion in 1972 to about \$420 billion in 2002. Total pharmaceutical R&D expenditures in the largest industrialised bloc, the US the EU and Japan, more than tripled between 1990 (Euro 18 billion) and 2002 (Euro 55 billion).<sup>22</sup>

On the other hand, as of the mid 1990s the pharmaceutical industry finds it increasingly difficult to introduce drugs that are truly innovative.

The dramatic increase in R&D expenditure, particularly in the different phases of clinical trials, did not result in a proportionate increase in the introduction of new drugs (or more accurately new molecular/chemical entities - NMEs or NCEs), but rather the contrary.

In fact, during the late 1990s and early 2000s we experienced a decline in the number of new drugs approved for market use - from 53 NMEs during 1996 to a level of about 20 NMEs in 2000.<sup>23</sup>

Despite the developments in the fields of diagnostics, bioinformatics, delivery systems and the ability to target and isolate specific genes, proteins and receptors, there is no coherent business model which can claim "victory" in the attempt to translate all of this potential into final - on the market- products.

Research-based pharmaceutical companies also tend to focus on the launch of "me-too" drugs and on the development of new delivery systems for existing drugs, such as in the case of anti-depression drugs.<sup>24</sup>

Moreover, generic-based companies have become much more aggressive, and more successful, in challenging the patents of original drugs.

**Finally, in recent years we are witnessing a "meltdown" in the balance of the pharmaceutical patent system** which is characterized by fierce legal patent disputes and retaliation.

Generic-based pharmaceutical companies are becoming much more strategically proactive and successful in challenging the patents (and "piggy-back" patents) of original drugs in the lucrative markets, i.e. the US and the EU.

According to the US Federal and Trade Commission (FTC), between 1998 and 2001 the FDA granted to more than 31 generic drugs 180 days of market exclusivity, based on successful patent challenges [Section 505(j)(5)(B)(iv) of the Federal Food Drug and Cosmetic Act grants 180 days of marketing exclusivity to the first generic applicant, who in the course of submitting an abbreviated new drug application (ANDA) to the FDA, is able to challenge the validity of the patent of the original drug].<sup>25</sup> Prior to this date, between 1992 and 1998, the FDA did not grant 180 days of market exclusivity to any generic drug. Two notable examples of the shift in the strategy of generic companies are the cases of Ranbaxy - the Indian-based company - challenging the patent of Lipitor, Pfizer's best selling cholesterol drug, and Dr. Reddy's Laboratories, another Indian-based company - challenging the basic patent of Zyprexa, Eli Lilly's best selling schizophrenia drug.<sup>26</sup> Overall, the FTC study found that generic-based companies have a success rate of nearly 75 percent of patent litigations in the US.<sup>27</sup>

Recently, however, research-based pharmaceutical companies, such as Pfizer, Merck and Eli Lilly have begun to retaliate against generic companies that challenge their patents by adopting the strategy of "**authorized generics**". This strategy aims to nullify the substantial prospective profits of a generic company that has been granted 180 days marketing exclusivity (on the basis that it was the first to challenge the patent of the original drug) by granting another "friendly" generic company a license to produce a generic substitute to the original drug.<sup>28</sup> In other words the strategy of authorised generics speeds up competition in the generic market, at the expense of the exclusivity period of both the originator and the generic company (that was entitled to the 180 days of marketing exclusivity). However, although this strategy is clearly based on commercial interests, it is still positive from the point of view of the public who can now enjoy a wider selection of generic drugs at cheaper prices.

One of the most recent examples (August 2004) of the "authorised generics" strategy and its implications is the dispute between Mylan Pharmaceuticals, Procter & Gamble and the FDA concerning the drug Macrobid for the treatment of urinary tractions.<sup>29</sup> Mylan was the first generic company to challenge the patent of the drug and therefore was entitled to the 180-days market exclusivity. However, Procter & Gamble has partnered with another generic company, Watson Pharmaceuticals, to manufacture a generic substitute to the drug, thereby effectively eliminating Mylan's 180-days exclusivity period. Mylan sued the FDA for failing to enforce the 180-days exclusivity policy and requested a preliminary injunction in the U.S. District Court to prevent Procter & Gamble from partnering with Watson Pharmaceuticals. U.S District Judge, Irene Keeley referred to Mylan's case as "extremely compelling" and said that

Congress had left "a gaping black hole" in the Federal Food Drug and Cosmetic Act by apparently failing to anticipate the possibility of authorized generics.<sup>30</sup> However, on 30 August 2004 Mylan abruptly dropped its federal lawsuit against the FDA, with no specific explanation.

It is because of these circumstances that data exclusivity is becoming increasingly dominant as an additional IP layer of protection which affects both research-based and generic-based pharmaceutical companies.

### **3. The effect of data exclusivity on the ongoing battle between research-based and generic-based pharmaceutical companies.**

With respect to the effect of data exclusivity on generic companies, since these companies lack the financial resources for creating a complete registration file, they often look upon data exclusivity as yet another extension of the overall exclusivity period of pharmaceutical products. The European Generic Association argues that "data exclusivity merely extends the originator company's market monopoly over a product by not allowing the authorities to process an application for marketing authorisation".<sup>31</sup> A similar view was also expressed by James P. Love, of CPTech, who argued that "many health care experts believe the current five years of market exclusivity (in the US) for health registration data is excessive, and perhaps even unnecessary, given the opportunities for market protection which are available under patent and Orphan Drug laws."<sup>32</sup>

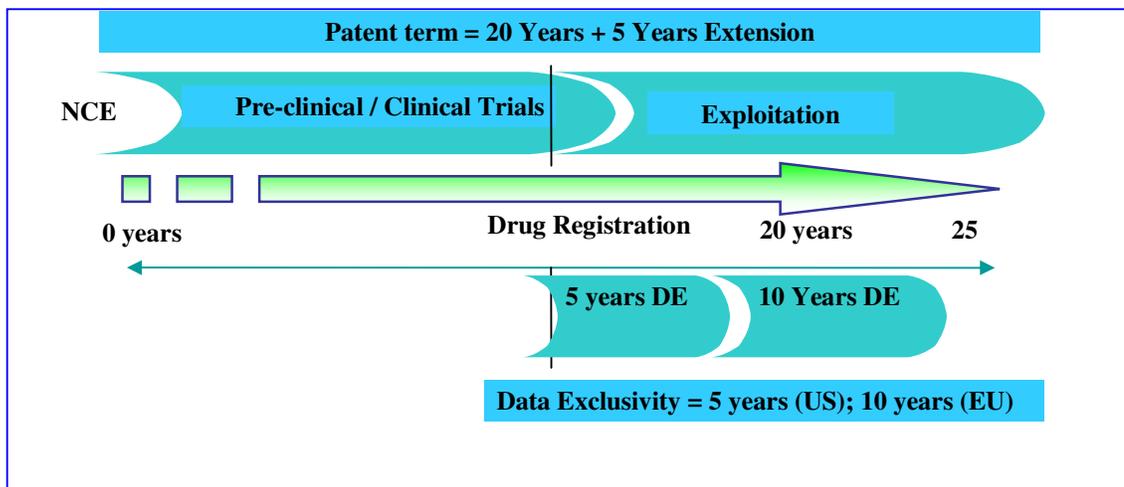
This raises a very interesting economic question about the extent to which the term of data exclusivity extends beyond the term of patent protection.

Empirical evidence is still insufficient. Yet, it is logical to assume that, for the majority of drugs, the maximum period of data exclusivity (in the EU and the US 10 years and 5 years respectively from the day of registering the drug) is shorter than the 20-year patent term. One has also to bear in mind that a pharmaceutical patent may be extended in Europe and in the US by an additional period of up to 5 years. In the EU, regulation EC 1768/92 allows a pharmaceutical company to extend the term of its patent by an additional period of up to five years, as long as the effective patent life does not exceed fifteen years from the date of marketing authorisation (this mechanism is called a Supplementary Protection Certificate or SPC).<sup>33</sup> In the US, the 1984 Drug Price Competition and Patent Term Restoration Act (known as the Waxman-Hatch Act) increased the effective patent term of protection by an additional maximum period of five years.<sup>34</sup> These policies aim to allow originators to extend the effective term of patent protection for a new pharmaceutical product, given the gap between the time a patent is granted for a new molecule and time the drug is authorized for marketing.

An additional distinction that further complicates the above calculation is between *data exclusivity legislation* and *marketing exclusivity legislation*. The exclusivity period generated by the former is usually longer than the one generated by the latter. For example, let us assume that a developing country has data exclusivity legislation. Since a generic applicant would be able to rely on the registration files of the original drug only after five years from the time the original drug was registered, this means that the originator effectively has a market exclusivity of five years *plus* the time it

would take the regulatory authorities in that country to approve the generic application. In the case of market exclusivity legislation, a generic applicant would be allowed to rely on the registration file of the original drug prior to the expiration of five years in order not to delay its entry into the market. As discussed later in the paper, the new European legislative formula is a combination of data exclusivity and market exclusivity.

**Figure 1 - Market exclusivity periods generated by patents and data exclusivity legislation**



That said, there are three potential cases in which data exclusivity can affect the overall period of market exclusivity.

**The first is a situation in which the development period of a given drug is particularly long**, in which case the effective commercial term of patent protection is shorter than the term of protection provided by data exclusivity (or in other words  $T_{patent\ protection} < T_{data\ exclusivity}$ )

A study by IMS Health (2001) on the effect of data exclusivity in Europe found that "very few high-selling drugs gain further marketing monopoly from the provision afforded by data exclusivity" and that "only drugs that do not have granted Supplementary Protection Certificates or took an exceptionally long time to traverse the R&D process gain significantly from the data exclusivity provisions".<sup>35</sup>

For example, as shown in Table 1 below, in the US the patent expiration date (2004) of Eprex (Epeotin Alpha) - Jansen Cilag's blockbuster drug for severe anemia - is shorter than the period of data exclusivity granted to this drug (2005). This is also the case with Arava (Leflunomide) - Aventis' drug for the treatment of Rheumatoid arthritis.

**Table 1: Patent and data exclusivity expiration periods in the US for selected drugs**

PRODUCT	Taxol (Paclitaxel)	Epex (Epeotin Alphah)	Arava (Leflunomide)
PURPOSE	<b>Breast Cancer /Ovarian Cancer and others</b>	<b>Severe Anemia</b>	<b>Rheumatoid arthritis</b>
U.S.MARKET APPROVAL	<b>Discovered in 1962 Approved in 1994/1998</b>	<b>2000</b>	<b>1998</b>
U.S. Patent Expiry	-----	<b>2004</b>	<b>2001</b>
U.S. DE Expiry	<b>2004 (Orphan Drug)</b>	<b>2005</b>	<b>2003</b>

*Calculations are based on the FDA's Orange Book*

**The second case involves drugs that do not enjoy a "foolproof", or even partial, patent protection.** The most celebrated example is Taxol - Bristol-Myers Squibb's anti-cancer drug. The drug, which was discovered by the National Cancer Institute in 1962, and whose active ingredient is based on the natural and well documented substance of the Pacific Yew bark, was licensed exclusively to BMS in 1991 for commercial development.<sup>36</sup> In the case of Taxol, data exclusivity and Orphan drug exclusivity provide the key protection layer.

**The third and final case concerns the generic substitutes of biotechnology drugs,** i.e. drugs that are based on cellular and bimolecular processes, as opposed to "conventional" drugs that are based on chemical entities.

With the expected patent expiration of the first generation of biotechnology drugs (by 2006 approx. 11 biotech drugs will experience patent expiration, the market value of which is more than \$US 13 billion in annual sales) there is now an open question as to whether bioequivalence tests apply to biogeneric drugs.<sup>37</sup>

In contrast to the process of creating a generic substitute to a "conventional" drug, which is quite a straightforward process based on duplication (or reverse engineering), the creation of a generic substitute (bio-generic) to a biotech drug is much more complex and novel at present.. Arguably, in the case of biotech drugs that are based on therapeutic proteins, it is not enough to demonstrate that a generic drug is bioequivalent to the original drug, since there may still be substantial clinical differences between the original and biogeneric drugs that require additional investigations and data collection via clinical trials.<sup>38</sup>

Admittedly, both the FDA and the EMEA have yet to provide clear-cut guidelines and regulations for the approval of biogenics by way of relying on the registration files of the original product. The question here is not only one of exclusivity but also, and much more importantly, of public health. As indicated by Mr. Lester M. Crawford,

Acting Commissioner of Food and Drugs, Department of Health and Human Services, in his testimony before the Committee of the Judiciary, U.S Senate (23 June 2004):

FDA believes that follow-on proteins, like the advent of generic drugs, may hold the potential for greater access to therapies and meaningful savings for consumers. We acknowledge that approvals of follow-on versions of more complex products are likely still years away, and would require resolution of serious scientific, legal, and policy issues. Furthermore, we recognize that the limitations inherent in the authorities related to the PHS Act differ from the authorities available to consider some biologic products regulated as drugs under the FD&C Act. Yet we also believe that it is in the interest of the public health to provide meaningful opportunities for thoughtful public discourse on this subject as the science progresses. Today's hearing is an important part of that discussion and I thank Chairman Hatch for holding it.<sup>39</sup>

For example, in April 2004, Sandoz, the generic arm of Novartis, launched a legal action against the European Commission with regard to the latter's hesitation to approve Sandoz's version of Omnitrope, a human growth hormone. The Commission, concerned about public health safety, delayed the approval of Sandoz' generic drugs despite the June 2003 recommendation of the EMEA's Committee for Proprietary Medicines to approve it for market use.<sup>40</sup>

In other words, if the bioequivalence process does not apply in full or in part to the process of approving biogenerics then a whole new set of questions emerges about the extent to which the regulatory authorities are allowed to disclose the confidential data contained in the registration file of the original biotech drug in order to speed up generic competition.

Referring to the problem of data exclusivity and bioequivalence tests in biotech drugs, BIO, the trade association representing biotech companies in the US, argues:

Generic companies have voiced a desire to have a generic biologic. Superficially, generic competition seems inevitable, although analysis of this proposal suggests that many problems will arise in the process, including providing definitions of equivalence. There already are drugs in the marketplace that are similar in chemical or biological structure, however, when tested in clinical trials they have different clinical indications. Clearly, then, it is inappropriate to have abbreviated bioequivalence determination for such products by the Food and Drug Administration (FDA). Currently, a determination that two products are bioequivalent is not appropriate, consequently generic biologics is not something FDA looks forward to implementing...BIO would like to see ten-year data exclusivity in the United States - two times the arbitrary five-year period currently operative in this country. The longer exclusivity period may be viewed as encouraging innovations after a drug is on the market. One important objective of data exclusivity is to encourage firms to continue to do research and develop additional clinical indications once a drug is on the market. This goal is served better by a significant amount of exclusivity time, and it is not clear that five years is enough to encourage such activity".<sup>41</sup>

#### **4. Data Exclusivity in the Context of EU Enlargement**

The December 2003 amendments to the EU's data exclusivity legislation were part of a wide "package" of proposed changes aimed at substantially modifying the regulatory framework governing the pharmaceutical industry in Europe.

The calls for changing the current state of affairs in the European pharmaceutical industry were based on two major factors:

- 1) The urgent need to harmonise, as much as possible, the European pharmaceutical market, following the expansion of the EU.

2) The fact that the European pharmaceutical industry has become much less competitive as compared to the US pharmaceutical industry.

For example, compared to the US, the innovative strength of the pharmaceutical industry in Europe has declined over the years. The share of European countries in the development of NCEs declined from about 65 percent during the 1960s to about 40 percent in 2000 (Table 2).<sup>42</sup>

One possible explanation for this decline is the fact that, since the late 1990s, the pharmaceutical industry in Europe allocates less financial resources to R&D projects relative to the US.

The average R&D expenditure by the US pharmaceutical industry in 2000 and 2001 (Euro 23 billion and 26 billion respectively) exceeded that of Europe's (Euro 17 and 19 billion respectively) and Japan's (Euro 7.5 billion).<sup>43</sup> R&D expenditure as a percentage of sales is also higher in the US. In the 1990s it was estimated at about 15 percent in the US and 11 percent in Europe.<sup>44</sup>

**Table 2 Number of NCEs developed between 1950 and 2002**

Period of 1950 – 1989			Period of 1989 – 2002		
Origin	NCEs	% of Total	Origin	NCEs	% of Total
USA	788	35.34	Europe	255	41.26
Japan	236	10.58	USA	195	31.55
Germany	232	10.40	Japan	153	24.76
France	227	10.18	Others	15	2.43
Switzerland	227	10.18	<b>Total</b>	<b>618</b>	
UK	153	6.86			
Italy	121	5.43			
Belgium	114	5.11			
Sweden	59	2.65			
Holland	32	1.43			
Denmark	31	1.39			
Austria	9	0.40			
Ireland	1	0.04			
<b>Total</b>	<b>2230</b>	<b>100.00</b>			
<b>Total Europe</b>	<b>1206</b>	<b>54.08</b>			

**Source:** Pugatch, M. (2004), *The International Political Economy of Intellectual Property Rights* (Edward Elgar: London), Figure 4.4

For that purpose the European Commission established, on 26th March 2001, the High Level Group on Innovation and the Provisions of Medicines (also known as the G10 Medicines).<sup>45</sup> The Group's mandate was to propose a new agenda to improve the framework for competitiveness in the pharmaceutical industry and to harness its power to deliver on Europe's health-care goals.

Based on the Group's recommendations, in its July 2003 communication the Commission proposed a mandatory data exclusivity period of 10 years for all new pharmaceutical products that are registered under the mandatory pan-European 'Centralized Procedure'.<sup>46</sup> Also, the Commission proposed to grant an extra year of protection for new indications of original medicines (this is usually referred to as the 10+1 formula).<sup>47</sup> As to the registration of pharmaceutical drugs at national level (so-

called 'Decentralized Procedure') based on the decision of the European Council, the Commission recommended harmonizing the period of data exclusivity to 8 years with an additional 2 years of market exclusivity (this is usually referred to as the 8+2 formula).<sup>48</sup> One has to bear in mind that prior to the December 2003 resolution, the period of data exclusivity at the national level varied between the member countries (and EU candidates at the time). For example, a 10-year period of data exclusivity was granted in Germany, France, the UK and the Netherlands, while a 6-year period was granted in Austria, Greece, Spain, Estonia and Latvia (Poland has a data exclusivity period of 3 years).

Finally, the Commission recommended that generic companies be legally entitled to make commercial experiments in patented pharmaceutical drugs as part of the process of obtaining marketing approval for generic substitutes (so called 'Bolar' provisions)<sup>49</sup>. The underlying logic of this proposal is to reduce any delays in the launch of a generic drug once the patent of the original drug expires.

In its meeting of 17 December 2003 the European Parliament adopted a compromise, known as the '8+2+1' formula.<sup>50</sup> According to this formula new pharmaceutical products would be entitled to 8 years data exclusivity, 2 years of marketing exclusivity (in which generic companies would be allowed to engage in Bolar-type activities) and an additional year of protection for new indications of existing products.\*

At first glance, the 8+2+1 formula strikes a balance between the diverging interests of the pharmaceutical sector, with some added advantages to research-based companies. That said, there are still some fundamental issues that need to be addressed before intra-EU harmonization can take place de-facto.

For example, the decision to implement Bolar-type provisions is likely to open a whole new 'can of worms' with regard to patent protection in Europe. On the one hand, the WTO dispute settlement body had made it clear (March 2000) that Bolar provisions are consistent with the WTO patent regime (the result of the highly celebrated patent dispute between the EC and Canada).<sup>51</sup> On the other hand, the implementation of EU Bolar provisions both de jure and de facto, require changing or interpreting the European patent regime and the procedures of registering generic substitutes in a much more coherent and clear manner than currently stated in the decision. Campolini argues that "as far as the content of the new legislation is concerned two remarks can be made. First, the legal clarity has been affected by political considerations and as a consequence, there are a number of incomplete formulations. The practical implementation of the system will therefore be a crucial point in the future".<sup>52</sup> One can only learn from the American experience (from which the Bolar mechanism originates) as to how complex and such a system is.<sup>53</sup> This issue would require some serious discussions and further studies.

As explained earlier, another huge problem is the looming debate over the actual and 'definitional' similarity between biotechnological drugs and their generic follow-ups (bio-generics)<sup>54</sup>. For this new class of drugs, data exclusivity is going to play a pivotal

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\*. The difference between data exclusivity and market exclusivity was explained in discussed in section 3

role, possibly more than patents. Unfortunately, the proposed legislation, which focuses primarily on chemical formulations rather than biological ones, is not going to solve this issue, not least because there is still some way to go before bio-generic drugs could penetrate the market.

### **5. Data Exclusivity as international North-South Issue**

The debate over the scope and term of data exclusivity is rapidly spilling over to other countries, particularly advanced developing countries with established R&D capabilities.

As briefly mentioned earlier in the paper (section 1), it is this author's view that the ambiguity of TRIPs Art. 39.3, drove the US, and to a lesser extent the EU, to actively seek the establishment and implementation of data exclusivity legislation of a US standard in many developing countries.

This is done through two major mechanisms:

- i. FTAs and RTAs between developing countries and the US/EU.
- ii. Using trade relations tools, such as the US 'Super 301' and the EU's Trade Barriers Regulation (EC 3286/94), as a leverage on developing countries to put effective data exclusivity legislation in place.<sup>55</sup>

**With regard to the first mechanism**, we can argue quite safely that since 2000 there is growing evidence suggesting that regional and bilateral trade agreements - between the US and EU on the one hand and developing countries on the other hand - are based on *TRIPs* + provisions, including those in the field of data exclusivity.

For example, an OECD study (2002) argues that most "RTAs dealing with intellectual property rights have more far-reaching provisions than those found in the WTO Agreement on Trade-Related Aspects of Intellectual Property Rights".<sup>56</sup> Similarly, a draft study by the World Bank (2004) finds that "in investment and intellectual property rights, North-South agreements have enjoyed considerable success in promulgating comprehensive new rules that go beyond multilateral agreements" and that the "embedded IPR in all FTAs are essentially 'TRIPs plus'.<sup>57</sup> Other studies by Abbott (2004), Viva-Eugui (2003), and Roffe (2004) have also reported on the various elements that are subject to *TRIPs*+ provisions, such as patents, data exclusivity and copyrights<sup>58</sup>

In the case of data exclusivity, the US is the "demandeur", in the sense that FTAs and RTAs between the US and developing countries are based on the data exclusivity standards of the former. In other words, it would seem that the regional and bilateral negotiating tracks lead developing countries to agree to commit to a level of data exclusivity legislation that is substantially higher than the level of TRIPs.

To recall a few examples, Art. 15.10 of the Central American Free Trade Agreement (CAFTA), of May 2004, requires the establishment of data exclusivity legislation, consisting of a minimum 5-year protection period, non-disclosure and non-reliance, including cases in which marketing authorisation was granted to a third party in another country.<sup>59</sup> Art. 17.10 of The US-Chile FTA (2003) places similar mechanisms of data exclusivity (5-years, non-reliance/non-disclosure), as is Art. 16.8 of the US-

Singapore FTA (2003) and Art.17.1 of the US-Australia FTA (2004)<sup>60</sup>. That said, as Roffe indicates, FTA data exclusivity provisions between the US and developing countries are not identical.<sup>61</sup> Variations are either a result of the US becoming more specific over time (for example, the difference between Jordan and Singapore) or the ability of developing countries, such as Chile, to limit some of the US demands. Compared to the US, the IP provisions of new-generation FTAs (so called Association agreement) between the EU and developing countries ( Jordan, Israel, Chile) are much more general and less issue-specific. These provisions usually refer to the need to provide "adequate and effective protection of the highest international standards including effective means of enforcing such rights".<sup>62</sup> In some recent FTAs, such as in the case of Chile (Art. 169) the agreement enumerates the IP provisions that require protection, including "protection of undisclosed information and protection against unfair competition as referred to in Article *10 bis* of the Paris Convention for the Protection of Industrial Property (Stockholm Act 1967)".<sup>63</sup>

**The second mechanism - the threat of trade retaliation** - is currently being used by the US and the EU against developing countries, in which the absence of data exclusivity legislation results in a serious commercial clash between the local subsidiaries of research-based multinational pharmaceutical companies and powerful local generic-based companies, that are often perceived as "national champions".

Israel is one notable example, in which there is a huge clash of interests between the multinational research-based pharmaceutical industry, backed by the United States Trade Representative (USTR), and the local generic industry, represented by Teva - the biggest generic multinational pharmaceutical company in the world.<sup>64</sup>

Lack of data exclusivity in Israel caused considerable commercial losses to the research-based companies who had registered these medicines. According to Pharma-Israel, the trade association representing multinational research-based pharmaceutical companies operating in Israel, at least 15 original products registered in Israel were almost immediately exposed to generic competition due to the absence of data exclusivity<sup>65</sup>. The association also reports that since the year 2000, at least 11 products, to which data exclusivity is the primary mode of protection, were not registered in Israel<sup>66</sup>)

Consequently, the absence of data exclusivity legislation in Israel became one of the major commercial disputes between the US and Israel. As noted in the 2002 Special 301 Report of the USTR:

And, most significantly, although Israel has been obligated since January 1<sup>st</sup> 2000 to provide data exclusivity, it has failed to do so. This policy places it at odds with other OECD-level economies and many of its neighbors that have met their TRIPS Article 39.3 obligations.<sup>67</sup>

The ongoing pressures by the US and the research-based pharmaceutical lobby on the government of Israel resulted in the establishment of an inter-ministerial committee for the enactment of a data exclusivity bill. The inter-ministerial committee issued its recommendations in February 2004 and the Government approved these recommendations in September 2004.<sup>68</sup>

However, the USTR argued that the proposed bill does not meet the minimum US-standard, as indicated by "301 Watch List Report" of 2004:

"On the key issue of data exclusivity, Israel's actions have not met U.S. expectations. In April 2004, the Israeli Government developed a set of recommendations on data exclusivity that recognized for the first time the need to provide a minimum five-year period of protection for confidential test data for innovator firms in Israel. However, several serious shortcomings in the recommendations would severely compromise the data protection afforded by Israel, keeping it far short of OECD-level standards for data exclusivity".<sup>69</sup>

According to the USTR, the key problem of the proposed data exclusivity bill is that it allows generic-based pharmaceutical companies to rely on the registration data of the original drug for export purposes, as indeed argued by the Government of Israel. The Government justifies this decision by stating that it is committed to maintaining the advantage of its local generic industry to be able to export generic products abroad.<sup>70</sup>

Roffe reports on heavy pressures on the Chilean government by the USTR and the multinational research-based pharmaceutical companies during the final phase of the FTA negotiations between the US and Chile.<sup>71</sup>

Another example is the launch of an investigation by the European Commission against Turkey in December 2003, following a complaint by the European Federation of Pharmaceutical Manufacturers and Associations (EFPIA). The investigation concerns obstacles to trade allegedly caused by Turkish practices and measures involving lack of transparency, discriminatory application of the pharmaceutical import, sales and marketing system, including a "lack of protection of commercially sensitive data submitted as part of the marketing approval procedure".<sup>72</sup>

Recently the debate over data exclusivity was also "exported" to India, which is now undergoing a change in legislation as part of its obligations under TRIPs to strengthen its pharmaceutical IP regime.<sup>73</sup>

## **6. Conclusions and suggestions for further research**

It would seem that the debate over data exclusivity marks a shift from the conventional debate over patent protection and drug prices. This debate, which involves both developed and developing countries, is characterized by political and economic interests, as well as by safety issues that guarantee to make it one of the more interesting subjects on the IP discussion table.

Nevertheless, there are two major difficulties associated with the issue of data exclusivity.

First, since data exclusivity is a new form of protection there are still significant disagreements on what this form of IP protection encompasses.

For example, what is the difference between data exclusivity and market exclusivity in terms of IP legislation? Should data exclusivity be part of the IP form of trade secrets, as suggested by TRIPs, or should it be part of pharmaceutical regulatory legislation, as in the cases of the EU, the US and the different FTAs? What should be term of data exclusivity? Do clinical trials undertaken by pharmaceutical companies for the purpose of introducing new indications of existing drugs fall under the category of "considerable efforts", and hence require data exclusivity? What type of activities fall under the category of reliance?

All of these questions require much more in- depth discussion.

Second, there is a need for much more concrete empirical data in order to assess the implications (positive and negative) of data exclusivity.

Here there are few dimensions that require further research:

- How many drugs in a given country are sensitive to data exclusivity protection in terms of the exclusivity period? In other words in which cases would data exclusivity extend beyond the term of patent protection?
- How many drugs rely on data exclusivity as their primary mode of IP protection?
- What are the implications in terms of the costs of drugs as a result of data exclusivity legislation in a given country?
- How many drugs are not registered in a given country due to the absence of data exclusivity?
- As a result, what are the implications in terms of competition in a given market and public access to existing medicines?
- What is the linkage between data exclusivity and investments in clinical trials?
- How would data exclusivity legislation influence the balance between pharmaceutical research-based companies and generic-based companies in a given country?
- To what extent does data exclusivity legislation in one country affect the ability of a generic industry in another country to compete in the global markets?

Paradoxically, the ambiguity of the TRIPs agreement on the issue of data exclusivity resulted in FTAs and RTAs that require data exclusivity legislation according to the US or European standards. Thus, developing countries find themselves in a peculiar situation in which they are committed to implement a much more operational data exclusivity legislation, sometimes without fully comprehending its implications (again, both positive and negative).

A more informed discussion on data exclusivity - that is based also on empirical findings - can thus help us to conclude what is an acceptable prototype model of data exclusivity to be adopted at the multilateral level, , including the provisions contained in Art. 39.3 of TRIPs.

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