

Mitain Patel

**The Transition from Patented Drugs to Generics:  
TRIPS Constraints and Policy Options**

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## **About the Author**

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## **Abstract**

The introduction of low-cost generic drugs upon patent expiry is an extremely contentious issue, with public health activists accusing pharmaceutical companies of profiteering at the expense of public health provisions, whereas pharmaceutical companies insist that stronger and lengthier protection for their intellectual property rights is necessary for them to sustain investments in research and development. This study is an overview of the transition from patent monopolies to free markets, studying the evolution of legislation and the mechanisms of introducing competition from generic pharmaceuticals once a patent expires.

The TRIPS agreement, due to come into force in January 2005, has major implications for countries that have not yet introduced intellectual property legislation, as it will require them to introduce a minimum standard of patent and data protection legislation. This study looks at the possibilities available to such countries regarding the transition process, and the effects that different legislative measures could have on their economies. It also makes some recommendations regarding measures that will facilitate the fastest and cheapest possible introduction of generic drugs following the expiry of a patent.

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## **Abbreviations**

ANDA: Abbreviated New Drug Application

CAFC: Court of Appeals for the Federal Circuit (United States of America)

EC: European Community

ECJ: European Court of Justice

EEC: European Economic Community

EMA: European Agency for the Evaluation of Medicinal Products

FDA: Food and Drug Administration (United States of America)

IND: Investigational New Drug

LDC: Least Developed Country

MHRA: Medicines and Healthcare products Regulatory Agency (United Kingdom)

NCE: New Chemical Entity

NDA: New Drug Application

PTE: Patent Term Extension (also known as Patent Term Restoration)

R&D: Research and Development

SPC: Supplementary Protection Certificate (Europe)

TRIPS: Trade Related Aspects of Intellectual Property Rights

WTO: World Trade Organisation

## **1. Introduction**

### **1.1 The Great Public Health Debate**

Patent protection for medicinal products has been the subject of much recent scrutiny in the media. Many claim that patents are responsible for elevating prices and thus restricting the availability of certain drugs used in treating preventable diseases, particularly in third world countries with limited healthcare funds.<sup>1</sup> Others, especially research-based pharmaceutical companies based in developed countries, insist that patent protection is essential for promoting continued innovation into new, more effective medicines.<sup>2</sup> The AIDS crisis is a particular issue bringing this debate to the attention of the public.

Whatever the arguments in this ongoing debate are, one thing is certain. The World Trade Organisation's ("WTO") controversial TRIPS<sup>3</sup> agreement is due to come into effect in 2005, ensuring that the majority of countries that have not already done so will be forced to introduce a minimum standard of intellectual property protection into their legislation, including certain elements of patent and test data protection. Many say that this will adversely affect public health provisions in developing countries, as it will allegedly restrict the production and availability of cheap generic drugs that these countries rely on to control disease. Although the compulsory licensing measures reaffirmed under the Doha Declaration of 2001<sup>4</sup> ensure that essential drugs can be made available at low cost, the successful use of such measures, especially in Brazil,<sup>5</sup> has been met with antipathy from certain developed countries, and there have been concerns that such opposition will discourage the use of this measure in the future, effectively undermining its intended purpose. Bilateral trade agreements between developed

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<sup>1</sup> KAMAL-SMITH, M., et al., 2002. Generic competition, price and access to medicines. *Oxfam Briefing Papers*, July 2002.

<sup>2</sup> CRESPI, R. S., 2003. IPRs under siege: first impressions of the Report of the Commission on Intellectual Property Rights. *European Intellectual Property Review*, 25 (6), 242-247

<sup>3</sup> Trade Related Aspects of Intellectual Property Rights: Annex 1C of the Uruguay Round Agreements completed in 1994. Full official text available at:  
[http://www.wto.org/english/docs\\_e/legal\\_e/27-trips.pdf](http://www.wto.org/english/docs_e/legal_e/27-trips.pdf)

<sup>4</sup> A full explanation of the Doha Declaration is available at  
[http://www.wto.org/english/tratop\\_e/dda\\_e/dohaexplained\\_e.htm](http://www.wto.org/english/tratop_e/dda_e/dohaexplained_e.htm)

<sup>5</sup> BBC News (2001) *Brazil to break AIDS patent*.  
<http://news.bbc.co.uk/1/hi/business/1505163.stm>

and developing countries have also been held responsible strengthening developing countries' patent regulations beyond that required under TRIPS, in some cases limiting the effectiveness of the WTO's compulsory licensing measures under Doha.<sup>6</sup>

High drug prices are not only a problem in the developing world. In countries where medicines are funded by the state through healthcare bodies such as the UK's National Health Service and Australia's Pharmaceutical Benefits Scheme, high drug prices can significantly impact healthcare budgets,<sup>7</sup> and thus these governments will aim to keep prices as low as possible while continuing to promote innovation.

## **1.2 Pharmaceutical Patenting and Regulation**

Research based pharmaceutical companies invest billions of pounds annually in developing new drugs and improvements to existing treatments.<sup>8</sup> Discoveries that have the potential to be developed into products are patented wherever possible. A basic patent will award the patentee an effective monopoly term of a minimum of 20 years. However, in the case of pharmaceuticals, most of this term is usually spent conducting tests and clinical trials to determine the drug's effectiveness and safety, and to convince regulatory authorities that the drug is fit for large-scale use on human patients. According to *Cunningham*, approximately 90% of drugs that enter clinical trials are not successful, and are either abandoned or researched further, modified and resubmitted for testing. Pharmaceutical companies therefore rely on the few drugs that are successful as their main source of income, using the profits to recover the large sums of money invested in research. Due to the limited amount of time available between marketing authorisation<sup>9</sup> and patent expiry, profits must be kept high if the company is to recoup its investments in such a

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<sup>6</sup> PALMEDO, M. and MAYNE, R., (2002). US Bullying on Drug Patents: One Year After Doha. *Oxfam Briefing Papers*, November 2002.

<sup>7</sup> DRAHOS, P., et al. *The FTA and the PBS: A submission to the Senate Select Committee on the US-Australia Free Trade Agreement*. Available at: <http://evatt.labor.net.au/publications/papers/126.html>

<sup>8</sup> CUNNINGHAM, R., 1998. Running with the Regulators. *Managing Intellectual Property*, 82, 16-31. ("*Cunningham*")

<sup>9</sup> Marketing authorisation is when the relevant regulatory body approves the drug for full-scale use on human patients.

short space of time. Patents for successful drugs are extremely valuable and can constitute a significant part of a company's asset portfolio.

### **1.3 Generic Drugs and Price Competition**

A generic drug is effectively a “copy” of an existing drug that is introduced by a third party “generics firm” after the originator's patent expires. As generics firms have much lower R&D expenses, they do not need to recuperate the same level of investment, and can therefore afford to sell their products at much lower cost, which the originator will not be able to match. Generic drugs have been the basis of low cost treatment for several years, and large-scale buyers of pharmaceuticals, including state healthcare authorities, will naturally favour the cheapest product. Originators have repeatedly claimed that their products are safer and more effective than generic equivalents, although there is yet no evidence to prove these claims, a fact that has been publicly confirmed by an official of the US Food and Drug Administration.<sup>10</sup>

The mechanisms of introducing generic drugs once a patent expires has been a much-debated issue in recent years, especially in Europe, which has recently seen two major changes in legislation and two high profile cases in the European Court of Justice.

The speed at which generic drugs are introduced to the market largely depends on legislation concerning patents and also the protection of test data submitted to regulatory authorities as part of the procedure for obtaining marketing authorisation.<sup>11</sup> This data is often the result of expensive and lengthy tests, requiring trials on both animals and humans. The exclusivity of this data would result in generics manufacturers having to repeat trials at considerable expense, presenting a considerable barrier to entry and significantly delaying the introduction of generic competition, allowing the originator to maintain its monopoly well beyond patent expiry. However, originators, usually large,

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<sup>10</sup> From a speech by Dr. Mary Fanning, associate director for medical affairs in the office of compliance at the FDA's centre for drug evaluation and research, in 1998. Cited in *Cunningham*.

<sup>11</sup> COOK, T., 1998, Maximising Chemicals Protection in Europe. *Managing Intellectual Property*, 76, 39-44.

research-focused multinationals, insist that the expenses incurred in producing these data must be recuperated, and therefore tend to favour strong data exclusivity measures.

Measures have evolved that allow rapid generic introduction following patent expiry whilst still providing adequate compensation to originators for losses incurred due to the regulatory process. These measures have become increasingly complex, and will be discussed in detail later in this study.

TRIPS, although fairly explicit in its requirements for patent protection, allows considerable flexibility for countries that are yet to introduce legislation protecting regulatory data. Although this flexibility allows countries to develop their own approach to this issue, it also presents a dilemma for countries yet to implement such legislation, as the models used in developed countries are subject to constant review and amendment, and even then may not be the most suitable option.

The purpose of this study is to analyse legislation in the developed world and its effect on company and market behaviour in respect of patent expiry and generic introduction, and suggest possibilities for legislative measures that would promote the best interests of developing countries yet to introduce such measures.

#### **1.4 Methodology**

This study is divided into two parts, the first being an analysis of European and US Law in respect of measures relevant to the transition between patent monopolies and free markets. These measures are patents, data exclusivity and regulatory procedures. The first two are forms of intellectual property, with data exclusivity being a *sui generis* form of protection within regulatory law. Regulatory procedures are important as they largely determine the barriers to market entry for manufacturers of generic drugs. This study includes a retrospective analysis of European law, also including key measures implemented in the US, which influenced the European decision making process. Also included is a comparative study of European and US law, highlighting some of the key differences, and some of the problems faced. Particular focus is paid to loopholes in US law, and some of the strategies firms use to exploit these.

The second part relates to the implementation of Article 39.3 of TRIPS, which specifies the requirements for the protection of test data as required under international law. The terms of the agreement are analysed, together with a brief study of market conditions in India. This enables the findings from the first part to be related to the terms of TRIPS and market conditions in an economically significant developing country to formulate recommendations that will promote public health and economic growth in the domestic pharmaceutical sector of such a country.

### **Part 1 – Legislative Review**

The research for this study was mainly centred on the analysis of EC Directives and European case law, thus taking a positivistic approach, extracting and analysing the relevant facts from the law. The effects of case law and public criticism in the development of legislation were also taken into account.

Articles and case comments relating to the subject were also analysed. As these were mainly subjective, this research took an interpretivist approach. These articles were used to help interpret the Law, in addition to studying its implications for the relevant parties involved. Articles available on the Internet were also used in determining foreign developments, particularly in relation to US.

EC Directives and case law were located by searching legal databases, notably WestLaw and Lexis-Nexis. Articles were also located by searching these databases, and by searching the online archives of well-known Intellectual Property journals. Articles and case comments, especially those relating to US Law, have been located by searching the websites of major IP law practices, which often provide legal updates and comments, and through regular internet search engines such as Google. Unlike major law publications, which are usually written by corporate lawyers and therefore favour the research-based sector, Internet websites are popular among activists who strongly support the generics lobby and are against strong intellectual property provisions, especially in the developing world. Using articles from various authors favouring both innovatory

and generics firms was beneficial in developing a balanced and objective understanding of this contentious debate.

There are some limitations to the methodology employed. Only a selection of high-profile US Case Law was used, although this adequately highlighted key features of US Law. US statutory law was studied using articles and reports to Congress, which provided detailed explanations of the concepts and provided useful case studies.

Certain UK and European journals were not accessible, which led to a limitation of the number of articles used in this study.

Studies relating to the behaviour of firms were conducted qualitatively through studying articles and news bulletins, and although this provided a general overview of the tactics used, an exhaustive quantitative study of firms' behaviour was not carried out.

## **Part 2 – Analysis of possibilities available under TRIPS Article 39.3**

As the wording of Article 39.3 is fairly ambiguous in its requirements, significant references were made to articles on this subject to provide possible interpretations for the terms under the Article, which was subsequently broken up into four distinct criteria for protection.

As the resulting recommendations are intended to promote both public health and economic development within developing countries' pharmaceutical sectors, it was decided that India was to be used as an example of a developing country. This was because India is an economically significant country with high profile public health problems, but also has a successful pharmaceutical industry. Assessing factors that contributed to this success was useful in predicting some of the requirements of generics industries in the developing world. Market conditions were assessed using articles from journals, news websites and online magazines, as well as from personal experience.

After studying the Indian market and the needs of its pharmaceutical industry, it was possible to relate some of the concepts studied in the first section of this study to a developing market such as India within the context of TRIPS. Recommendations were made by modifying selected concepts to suit the needs of

the Indian economy. The flexibilities offered by TRIPS, and the effects of different interpretations of Article 39.3 on certain practices were also studied.

The main limitations of this section of the study is that recommendations are made based on purely qualitative studies of firm and market behaviour, and that recommendations are often untested variations of existing practices. These recommendations are also based on unofficial interpretations of Article 39.3, due to the lack of case law clarifying the terms under the agreement.

## **2. Introduction to the Process of Drug Approval**

The process of getting a drug from the laboratory to the market is a long, expensive and complex one, and often forms a significant part of companies' R&D and marketing budgets.<sup>12</sup> There are various procedures for different types of new developments. For example, the process of approving a new chemical entity will be much longer and exhaustive than that for a new formulation or a generic equivalent of an existing treatment.

In Europe, among other jurisdictions, the different procedures are divided into three main categories:

*New Drug Applications* (“*NDA*”) largely concern the regulation of new chemical entities (“*NCE*”), which are newly discovered chemicals that may have desirable therapeutic characteristics. NDAs require the applicant to conduct and provide the results of lengthy tests and clinical trials. The tests are required by Article 8(3)(i) of EC Directive 2001/83 to include physico-chemical, biological or microbiological tests, and pre-clinical (toxicological and pharmacological) tests. These tests are usually carried out on animals, and have been subject to criticism from activists against the practice.

Compounds that are successful in pre-clinical testing are then approved for clinical trials, and are known as *Investigational New Drugs (IND)*. Clinical trials are carried out on human subjects, and are divided into four stages, each stage requiring more time and volunteers.<sup>13</sup> Phase I trials are carried out on healthy volunteers unaffected by any medical conditions, in order to prove the safety of the drug and to determine any possible side effects. After it has been determined that there are no detrimental side effects in the short-term (usually around a few months), Phase II trials can begin. These are designed to test the clinical effectiveness of the treatment, and are carried out on affected patients over around 2 years. If these are completed satisfactorily, Phase III trials are carried out. This

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<sup>12</sup> PhRMA (the Pharmaceutical Research and Manufacturers of America) estimates the process to cost on average US\$500 million over 15 years before a newly discovered chemical entity can be marketed as a medicinal product, although this will vary considerably according to individual circumstances. From *Cunningham*.

<sup>13</sup> <http://www.wellcome.ac.uk/en/genome/tacklingdisease/hg12b006.html>

is similar to Phase II but with a far higher number of trial subjects (sometimes thousands). This takes a long time, but allows the applicant to provide adequate and conclusive proof demonstrating the treatment's safety and effectiveness. As Phases II and III are carried out over several years, any possible mid-term side effects that may emerge would be seen in Phase I subjects. Mid to long-term side effects that are not immediately visible during initial testing can be disastrous to a company's reputation, as Chemie Grünenthal discovered in the 1950s when its antiemetic drug Thalidomide was found to cause birth defects when used on pregnant women. This was at a time when testing on humans was minimal, and current procedures have been designed to ensure that drugs are proven to meet stringent safety requirements before they reach the market. Modern clinical trials do not stop with a grant of marketing authorisation. Phase IV trials involve receiving and analysing feedback from medical practitioners, which allows the manufacturer and the authorities to continually monitor the treatment's performance, and to react quickly to any signs of previously undetected side effects.

*Abbreviated New Drug Applications (ANDA)* are applications to market generic equivalents of existing treatments. Such applications rely on the originator's test data and do not require the resubmission of data, but require that the originator's data is not protected and that the applicant can prove that the generic meets certain criteria such as bioequivalency to the original product. These criteria have been the subject of two cases in the European Court of Justice ("ECJ") and a recent change in legislation, and will be discussed in detail later. The purpose of abbreviated applications is to save generic producers from having to repeat clinical studies, thus lowering entry barriers for potential competition following patent expiry. ANDA provisions are crucial in preventing the needless repetition of tests, which is desirable on both economic and ethical grounds, as such tests cost millions of dollars and involve lethal animal testing as well as human trials.

*Hybrid Abridged Applications* are used when an applicant uses data previously submitted to the authorities (as with an ANDA) together with new data as part of an application. This is common for applicants who are applying for authorizations for new indications or other improvements to an existing treatment. New

indications include different dosage schedules and methods of administration. Significant alterations to an existing drug's chemistry are usually not eligible for hybrid applications, and will need to use the NDA procedure. Such an example is Thalidomid, a single optical isomer of thalidomide, rather than a racemic mixture as used in the controversial original drug. The new version, produced by US firm Celgene, is to be used in the treatment of leprosy, which is considerably different to the original use of thalidomide.<sup>14</sup>

## **2.1 Patent Protection and Regulatory Data Exclusivity**

Patents and data exclusivity are both commonly used to protect medicinal products, but the mechanisms of protection are considerably different.

Patents are effectively temporary monopolies granted in a particular jurisdiction in exchange for disclosing full details of an invention that is “novel, contains an inventive step, and is industrially applicable”.<sup>15</sup> Patents are normally valid for a period of up to 20 years, on the condition that periodic renewal fees are paid. As long as a patent is in force, the patentee has the right to exclude any third party from making, using, disposing (ie: selling), offering, importing or keeping the patented product without prior authorisation. Patents are not limited to end products, as processes can also be patented, preventing use by third parties. Such patents would also indirectly cover any direct products of a process.

A patentee effectively has exclusive rights to his invention throughout the life of the patent. In addition, the rights to a patent can be licensed, traded or sold. Patent protection is the strongest form of protection available for pharmaceutical products. However, the costs of protection are high, and the criteria for patentability are strict, and considerable numbers of patent applications fail as a result.

The protection of test data does not confer the same nature of protection as a patent, but the criteria for eligibility are also considerably different. In most

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<sup>14</sup> Doctor's Guide, 1996. *Thalidomide Submitted for NDAs for Use In Leprosy and AIDS Cachexia*. <http://www.pslgroup.com/dg/daa6.htm>

<sup>15</sup> Article 52(1) European Patent Convention

developed countries, any data that is produced by an originator and submitted in relation to a successful NDA shall be protected for a limited period (ten years in the EC). Data exclusivity, afforded through a *sui generis* provision within regulatory law, is automatic and does not require payment of renewal fees. As the criteria for protection are much lower than that for patentability, this measure effectively provides an additional layer of legal protection for innovative pharmaceutical companies, as if they fail to patent a successful drug, they can still obtain limited protection through the exclusivity of submitted test data, thus temporarily discouraging competition and reducing risk for innovatory companies, which is desirable on policy grounds as it encourages investment in R&D. It also provides a degree of protection if a patent should be subsequently invalidated for any reason, particularly as a result of litigation.<sup>16</sup>

Data exclusivity is especially important for firms that formulate medicinal products using unpatentable substances such as naturally occurring products, as this is often their only form of intellectual property protection preventing the entry of competition.

It is important to note that data protection does not confer a monopoly right, but prevents potential competitors using the originator's data as part of their own abbreviated applications. This means that a competitor can legally generate and submit its own test data as part of the procedure to obtain marketing authorisation for a competing product, which, if successful, can be launched in direct competition in the absence of any patent protection. Although data protection provides a barrier to entry, a competitor can still legitimately enter the market in the absence of patent protection if it thinks it can recoup its investment in reproducing the data, which is rare in reality, but in the case of the lucrative pharmaceutical market is always a possibility. Therefore, although data protection does offer limited protection for products that do not meet the criteria for patentability, it should not be relied upon as an outright substitute for stronger patent protection.

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<sup>16</sup> PUGATSCH, M.P., 2004. Intellectual property and pharmaceutical data exclusivity in the context of innovation and market access. *ICTSD-UNCTAD Dialogue on Ensuring Policy options for Affordable Access to Essential Medicines, Bellagio, Italy*. Available from: [www.iprsonline.org/unctadictsd/bellagio/docs/Pugatch\\_Bellagio3.pdf](http://www.iprsonline.org/unctadictsd/bellagio/docs/Pugatch_Bellagio3.pdf)

Test data, like patents, can also effectively be “licensed”, by giving consent to a third party to use the data (e.g.: for an ANDA or hybrid application) before the expiry threshold, possibly in exchange for a fee or another form of consideration.

The patent system and the regulatory process are not entirely independent. Due to the fact that a large portion of the life of drug patents is lost due to the length of tests, many countries have introduced measures to compensate patentees for this loss by extending patents beyond the 20-year limit. The original idea was originally conceived in the US, and is now present in the legislation of many developed countries. US legislation contains a provision that grants a Patent Term Extension (PTE), the length of which is related to the time that the drug spent in the clinical testing and regulatory process. Most PTE provisions offer a maximum extension period of five years from the end of the basic patent.

In certain countries, data protection is also affected by the concept of patent linkages, which means that a data exclusivity period need not extend beyond the life of the corresponding patent. This meant that if a drug patent expired, its test data would no longer be protected. There have been many complaints about this, especially from pharmaceutical firms and the lawyers that represented them.<sup>17</sup>

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<sup>17</sup> CAMPOLINI, M., 2003. Protection of Innovative Medicinal Products and Registration of generic Products in the European Union: Is the Borderline Shifting? *European Intellectual Property Review*, 2003, 25(2), 91-97 (“Campolini”)

### **3. The Evolution of Regulatory Provisions and the Patent Monopoly/Free Market Transition in the Pharmaceutical Sector.**

Until the 1960s, regulatory requirements were extremely lax by today's standards, and there were considerable procedural differences throughout Europe. Animal testing was the norm for testing drug safety, and human trials were used only sparingly.

In the early 1960s, the Thalidomide disaster sparked an outcry, as it was found that the methodologies used in testing were inadequate, and that small-scale human trials could have detected the side effects and prevented the disaster, which affected over 15000 fetuses.<sup>18</sup>

#### **3.1 The First Step Forward**

In 1965, the council of the European Economic Community (EEC) passed a harmonising directive, 65/65/EEC<sup>19</sup>, which considerably harmonised drug regulation procedures throughout EEC countries. Most importantly, it stipulated the information required by the relevant authorities before a drug could be approved for marketing.<sup>20</sup> These data requirements were designed to allow national regulatory authorities to effectively assess whether a drug was safe and effective in its intended use.

A notable feature of the legislation was Article 4(8)(a), which contained certain exceptions where data could be replaced by references to previous tests for products that already had an "established use". This provided a considerable advantage to generics firms, as they were simply required to prove that the originator's product was "established", and to provide references to the originator's data in order to gain approval for a competing product. It was argued that these exceptions put innovatory firms at a significant disadvantage, as there were no provisions for the protection of data submitted to authorities, and that

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<sup>18</sup> LINGHAM, A. (2000) *Thalidomide*. Available at: <http://www.chm.bris.ac.uk/motm/thalidomide/start.html>

<sup>19</sup> Council Directive of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products.

<sup>20</sup> Namely physico-chemical, biological or microbiological tests, pharmacological and toxicological tests, and clinical trials, as stated in Article 4(8).

drugs that did not obtain patent protection were vulnerable to copying. Also, owners of drug patents that only obtained marketing authorisation late in the patent's life had a very short time to recover their investment in development and testing before generic competition could enter the market.

In order to reduce differences in national regulatory systems caused by varying interpretations of Article 4(8), detailed requirements for testing procedures and the resulting data were laid out by EEC Directive 75/318.<sup>21</sup>

### **3.2 Roche v. Bolar and the Hatch Waxman Act**

In the early 1980s, a US patent infringement case took place that would ultimately bring about one of the most important pieces of legislation in the modern transitional process. The US had a system much more in favour of innovatory forms over generics, and generics producers had to repeat certain tests to obtain marketing approval from the FDA. In this case, Bolar Pharmaceutical Co. began conducting tests for a generic version of flurazepam hydrochloride. Flurazepam was covered by a patent licensed to Roche Products Inc. Roche brought a patent infringement action against Bolar.

US patent law contained an exception for *de minimis* use, which covered experimental use. A US District Court rejected Roche's claim on the grounds that Bolar's infringement of the patent in conducting the tests was covered under the *de minimis* exception. The CAFC<sup>22</sup> later reversed this decision after an appeal.<sup>23</sup>

Although this decision was not entirely unexpected, it gave momentum to a campaign to introduce groundbreaking legislation that promised "cheaper drugs today, better drugs tomorrow", promoting the interests of both the innovatory and generic pharmaceutical industries. This legislation was introduced in 1984 as the Drug Price Competition and Patent Term Restoration Act,<sup>24</sup> now more commonly

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<sup>21</sup> Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products.

<sup>22</sup> Court of Appeals for the Federal Circuit.

<sup>23</sup> Roche Products Inc. v. Bolar Pharmaceutical Co., 733 F.2d 858 (Fed. Cir. 04/23/1984)

<sup>24</sup> P.L. 98-417

known as the Hatch-Waxman Act.<sup>25</sup> It acted on the outcome of *Roche v. Bolar* by specifically stating that conducting tests and trials as part of the FDA regulatory process was covered under the *de minimis* exception, therefore allowing generics producers to conduct required tests before the expiry of the originator's patent. This concept is now widely known as a "Bolar" or "springboarding" exception. Bolar exceptions also led to the creation of an abbreviated procedure for generic drug applications, whereby such applications could rely on existing test data, providing they can meet the criteria for eligibility. This lowered entry barriers considerably, and encouraged generic competition upon patent expiry. Such ANDA procedures are now used worldwide.

The Act also made concessions in favour of innovatory firms by introducing Patent Term Extensions. This allowed the extension of patents based on the amount of time the drug spent in the FDA regulatory process. This extension would give a drug a maximum patent coverage of 14 years following marketing authorisation, but any extension could be no longer than 5 years.<sup>26</sup>

The Hatch-Waxman Act also introduced the concept of providing NDA applicants with a period of market exclusivity following marketing authorisation. This meant that the FDA would not consider any application for a generic competitor for five years following authorisation. This was an alternative protection measure for medicinal products that were not protected by patents, as the manufacturer would still have an opportunity to recover R&D expenses. Modern data exclusivity measures are derived from this concept, although there are variations in the scope of protection.

Finally, the Act introduced the "Orange Book" concept. This requires NDA applicants to state the patents that it believes will be infringed if a generic competitor is introduced during the life of the patents. The patents relevant to each approved pharmaceutical are then listed in a publicly available register.

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<sup>25</sup> Named after Henry Waxman and Orrin Hatch, the US Senators who originally advocated the act.

<sup>26</sup> SCHACHT, W. and THOMAS, J., 2002. Pharmaceutical Patent Term Extensions: A Brief Explanation. *CRS Report for Congress*, Penny Hill Press.

Springboarding and Patent Term Extensions have now been adopted by many developing countries around the world, but the Orange Book concept has not been as widely accepted.

### **3.3 Data Exclusivity in Europe**

Following much discontent from the innovatory pharmaceutical industry regarding the lack of protection for test data, and the resultant potential for “free-riding” by generic competitors, the EC issued Directive 87/21 in 1987.<sup>27</sup> This was a major overhaul of 65/65, and introduced several new concepts to the regulatory process. The most significant was the addition of a period of exclusivity for test data, whereby a generic competitor could not apply for an ANDA within this period. The period for protection was 6 years for non-high technology products, and 10 years for high technology products, including most biotechnology products. Unlike the US, which offered a period of complete market exclusivity for originators, generic applications would still be considered within the data exclusivity period if the applicant could supply their own data.

87/21 also stated that an ANDA can be made for a product that is “essentially similar” to a reference product of which the test data is no longer protected. The “essential similarity” threshold is not defined further, which led to much confusion regarding the conditions for eligibility for the ANDA procedure.

Another concern with 87/21 was the patent linkage option within Article 8(a)(iii) for non-high technology products. This allowed member states the option of introducing legislation that only protects data until the relevant patent expires. Innovatory firms had hoped for data protection beyond patent expiry to allow them a greater period of market exclusivity, allowing them to recoup the costs associated with the regulatory process. The implementation of patent linkages ultimately rested in the hands of national governments, who were effectively given the choice of favouring either innovatory or generic firms. According to

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<sup>27</sup> Council Directive 87/21/EEC of 22 December 1986 amending Directive 65/65/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products

*Campolini*, patent linkages were not readily accepted by original member states, but accession states in Eastern Europe readily implemented the concept into their legislation.

### **3.4 Europe follows Hatch-Waxman.**

The EC decided in 1992 to introduce Patent Term Extensions into its legislation.<sup>28</sup> The extension term under the regulation was favourable for innovators, and could last up to a maximum of five years.<sup>29</sup> As it was fairly rare for drugs to be approved within the first ten years of patent life, maximum extension terms were potentially frequent. US extension terms are calculated differently, equal to the period the drug spends in the FDA approval process, plus half the time spent in testing. The European term was subject to a maximum patent monopoly period of 15 years following marketing authorization.

Although Europe had chosen to adopt PTEs, it had still not introduced Bolar exceptions, thus strongly favouring innovatory companies. Although “experimental use” is not an act of patent infringement under the legislation of EC member states, certain states such as the UK did not see testing for regulatory purposes as experimental use.<sup>30</sup> Generics producers based in these countries were in a much weaker position than their North American counterparts, and often led to these firms carrying out tests abroad in order to avoid patent infringement.

### **3.5 Community Regulation – One Step Closer to a Single Pharmaceutical Market**

A major problem in the European Community was the variation in regulatory processes and patent laws, which led to inconsistencies between member states, and made applying for authorisation across Europe difficult. In 1993, the EC

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<sup>28</sup> Council Regulation (EEC) No 1768/92 of 18 June 1992 concerning the creation of a supplementary protection certificate for medicinal products

<sup>29</sup> Under Article 13 of the directive, the SPC extension term is equal to “the period which elapsed between the date on which the application for a basic patent was lodged and the date of the first authorization to place the product on the market in the Community reduced by a period of five years”

<sup>30</sup> *Monsanto Co. v. Stauffer Chemical Co* [1984] FSR 574.

decided to set up an agency that would be responsible for Community-wide regulatory approval.<sup>31</sup> This agency, the London-based EMEA, would be key in harmonising regulatory policy across Europe. All high technology products that would obtain 10 years of data exclusivity under Directive 87/21 must go through the EMEA.

Another policy reason for establishing the EMEA was to discourage firms from preventing parallel importing within the Community, which was a major hurdle to overcome if the Community was to behave as a single market. To encourage pharmaceutical firms to treat the Community as a single market, it was a condition of approval by the EMEA that the drug had to be marketed under a single trade mark throughout Europe. Although this disadvantaged firms by encouraging parallel importing, the benefits to firms of using a single regulatory procedure outweighed this single disadvantage. The only exception to the single trade mark rule was when a member state objected to a trade mark after it was submitted. An example is Hoechst Marion Roussel's trade mark Refluidan, which was rejected by the Spanish trade mark registry. The firm was allowed by the EMEA to use a similar name, Refluidin, in Spain. This is the only exception to the single trade mark rule to date.

The option of using either the centralised route or separate national routes to approval has allowed for a certain degree of flexibility in Europe. In addition, competition between the EMEA and national agencies has led to the two making their best efforts to meet the needs of applicants and to offer a good service. Two anonymous studies comparing the FDA and the EMEA<sup>32</sup> found that 78% of FDA applicants felt that they had been held up by the FDA, whereas 94% of EMEA applicants were either satisfied or very satisfied with the standard of service. Miller subsequently states in his study that the EMEA is "(more) effective and cheaper" than the FDA.

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<sup>31</sup> Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products

<sup>32</sup> Quoted in *Cunningham* as being cited in a comparative study by Henry Miller, Stanford University.

### **3.6 The Meaning of “essentially similar”**

This was one of the questions asked by the English Court of Appeal to the ECJ in *R. v Medicines Control Agency ex. p. Generics (UK) Ltd.*<sup>33</sup> The ECJ was also asked to determine whether new indications should be protected independently for a period of 6 or 10 years from the date of filing of a hybrid application, or whether they should be protected only as long as the reference NDA. The ECJ decision<sup>34</sup> delivered a blow to the innovatory sector by ruling that new indications would only be protected until the exclusivity period covering the reference data expires. For example; if an innovatory firm obtained approval from the EMEA for a new dosage schedule for a drug 7 years after the original marketing authorisation, that new schedule would only be protected for the remaining 3 years of the exclusivity period. Any subsequent ANDA would cover the new indication as well as the original NDA.

The ECJ also provided three tests for essential similarity. A product must have “the same qualitative and quantitative composition in terms of active principles, the same pharmaceutical form and is bioequivalent, unless it is apparent in the light of scientific knowledge that it differs significantly from the original product as regards safety of efficacy”. These have since become the accepted requirements for eligibility for the ANDA procedure.

### **3.7 Do Bolar Exceptions violate TRIPS?**

Across the Atlantic, Bolar exceptions as originally conceived under the Hatch-Waxman act had become a welcome and established feature of US and Canadian law. Canada, with its booming generic drug industry, had also introduced legislation allowing stockpiling of generic drug supplies before the expiry of the originator’s patent. Europe, the world’s greatest opponent of Bolar exceptions, believed that stockpiling before patent expiry put originators at a disadvantage, and was in violation of European and International Laws. The EU issued a

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<sup>33</sup> [1997] 2 C.M.L.R. 201

<sup>34</sup> [1998] E.C.R. I-7967

complaint against Canada to the WTO,<sup>35</sup> alleging that stockpiling a generic during patent life, and Bolar exceptions themselves, were in violation of TRIPS. Article 30 of TRIPS allows exceptions to patent rights providing that they do not “unreasonably conflict with a normal exploitation of the patent and do not unreasonably prejudice the legitimate interests of the patent owner”. The WTO decided that the use of a patented chemical for testing purposes to satisfy regulatory requirements for marketing after patent expiry was covered by Article 30, but stockpiling was detrimental to the interests of the patent holder and therefore in violation of TRIPS. Although the EU had managed to prevent pre-emptive stockpiling, the decision was a relief to the US, as the WTO had sanctioned the legitimacy of Bolar exceptions.

### **3.8 The Current State of Play**

Directive 65/65 was replaced in 2001 by a codifying directive, 2001/83. This was only cosmetically different from the amended 65/65, and did not address any of the issues raised following the outcome of *Generics UK*, especially those relating to the protection of new indications.

In 2004, the ECJ handed down a decision based on questions asked by the English Court of Appeal in *R. v. The Licensing Authority ex. p. Novartis Pharmaceuticals UK Limited*.<sup>36</sup> One of the questions asked explicitly if a new indication (B) that was approved as part of the hybrid procedure under 2001/83 Article 10 (formerly 65/65 Article 4), referring to the original product (A), whether that indication would be covered by an ANDA for a generic product (C) that referred to the original NDA for (A). The decision followed that in *Generics*, saying that indications approved under a hybrid procedure would only be protected as long as the original product, and that the ANDA for (C) would cover and include the use of indication (B). Although this was not a great surprise, there were arguments in the press that the existing framework did not provide any incentive to improve a

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<sup>35</sup> EU v. Canada. WTO Decision WT/DS114/R

<sup>36</sup> [2004] 2 C.M.L.R. 26

treatment once it has been approved.<sup>37</sup> This prevented further research that could further improve the safety and efficacy of a drug after it was approved.

Shortly after the decision in *Novartis*, the European Council produced Directive 2004/27. This was the most radical overhaul of the existing legislation since data protection was introduced in 1987.

The most prominent feature of this directive is the new Article 10(6), which is the first time a Bolar exception has explicitly been introduced into European legislation. This is likely to have been influenced by the success of this provision in the US and the outcome of *EU v Canada*, where the legitimacy of Bolar exceptions had been confirmed. The European decision meant that all of the major developed powers with major pharmaceutical industries had introduced the legislation. Australia had already adopted the rule, and the Japanese Supreme Court had ruled that disallowing Bolar exceptions was contrary to the principles of its patent system.<sup>38</sup>

The introduction of Bolar exceptions resolved the confusion caused by varying definitions of “experimental use”. The UK did not recognise testing as experimental use, whereas Germany allowed testing as an exception from patent infringement.<sup>39</sup> The UK, however, did not require the submission of samples as part of an ANDA application, whereas other countries such as Germany and the Netherlands required sample submission, which is regarded as an act of patent infringement.<sup>40</sup> Sample submission is now permitted as an exception to patent infringement under Art. 10(6) of the amended Directive 2001/83.

Another feature that many welcomed was the scrapping of the “essential similarity” threshold. This was in turn replaced with the term “Generic of a reference medicinal product”. However, the given definition of a “generic medicinal product” in Art 10(2)(b) is almost identical to the definition of essential similarity as handed down by the ECJ in *Generics UK*. This means that although

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<sup>37</sup> COOK, T., 2003. Regulatory Data Protection of Medicinal Products in Europe. *Bio-Science Law Review*. Unknown. (“Cook”)

<sup>38</sup> Ono Pharmaceuticals Co. Ltd. V. Kyoto Pharmaceutical Co. Ltd., 1998. Case No. Heisei 10 (Ju) 153.

<sup>39</sup> Klinische Versuche (Clinical Trials) II. (Bundesgerichtshof Case X ZR 68/94)

<sup>40</sup> *Generics BV v. Smith Kline & French Laboratories Ltd* [1997] R.P.C. 801 ECJ

the term has been changed, the threshold for being classed as a generic remains essentially the same. The reasoning behind this change was to recognise new indications, as they have previously fallen under the ambit of “essential similarity” and therefore had not been eligible for additional protection.

Other measures include a uniform 10 year data protection term across Europe, instead of the variable 6 or 10 year term as before. This will undoubtedly simplify regulation procedures in Europe. As it is likely that the longer 10 year protection terms may frequently exceed patent life, patent linkages for regulatory data protection have also been removed. This means that any drug that fails to obtain a patent will still be eligible for data exclusivity under Art. 10. An exception to the 10 year protection period is that a potential competitor may submit an ANDA after 8 years, although the ANDA will not be approved until the 10 year protection has elapsed.

A significant move that has been welcomed by innovatory firms is the recognition and protection of new indications. If a new indication is submitted in the first 8 years of data exclusivity, the data exclusivity period for the original NDA, including the new indication, will be extended by one year, giving a total protection period of 11 years. Contrary to the US approach, new indications still do not receive separate protection from their original treatments. The one-year extension is not cumulative, and protection will last for no longer than 11 years. Some have responded saying that this is a step forward, but still does not go far enough.<sup>41</sup> This provision is commonly known as the 8+2+1 rule.

Since the original beginnings in 1965, the transition between patent periods and free markets for drugs has become increasingly complex, but regulation and legislation has become increasingly transparent, with clarification from both legal studies and case law. Many of the qualms of the industries involved have been addressed in the recent amendments, but in this fiercely competitive sector, there will always be conflict, and managers and lawyers on both sides will need new and innovative ways to find ways to further their interests.

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<sup>41</sup> CAMPOLINI, M., 2004. Fixing the Safety Net. *Patent World*, 2004, 162, 25-29

#### **4. A Comparative Scrutiny of EC and US Legislation**

The evolution of US and EC law regarding data exclusivity and generic introduction shares many similarities, but is decidedly different in many areas. Both have their own advantages and disadvantages. This section is a comparative study between the two, detailing some of the differences, and some of the problems still faced in the two jurisdictions.

After the recent changes in European legislation, basic ANDA procedures in the US and EC bear many similarities. The criteria for being eligible for the ANDA procedure are very similar in both jurisdictions. The EC criterion of “generic of a reference medicinal product” is defined in Art. 10(2)(b) of directive 2001/83 as amended,<sup>42</sup> and the equivalent US definition, now defined under the Section 21 Part 314.94 of the Federal Food, Drug and Cosmetic Act, states that the subject of an ANDA must be “the same as a listed drug”.<sup>43</sup> It must be noted that bioequivalency is implied in the US definition, and the FDA requires proof of bioequivalency as part of any ANDA.

Both the US and EC now provide springboarding exceptions for bioavailability testing and experimentation required to prove bioequivalency. This means that such tests may be legitimately conducted before the expiry of a patent. This provision is new in the EC, and it is likely that the EC will consider extensive case law from the US in disputes relating to this provision.

Despite these similarities, there are also many differences between US and EC procedures.

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<sup>42</sup> “generic medicinal product” shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

<sup>43</sup> According to the FDAC, “the term “same as” means identical in active ingredient(s), dosage form, strength, route of administration, and conditions of use.” A listed drug is a reference drug that is approved under the NDA procedure.

## **4.1 Data Protection Terms**

The EC now offers data exclusivity terms of ten years. This protects data submitted as part of NDAs by ensuring that the data is not used in the approval of an ANDA during the exclusivity period. This, however, does not prevent generic applicants obtaining and submitting their own data. The EC also allows generic applicants to submit an ANDA after eight of the ten years have elapsed, although the ANDA will not be approved until the exclusivity period has expired. The US provision adopts a different approach. Under the Hatch-Waxman Act, a drug that obtains marketing authorisation from the FDA is granted five years market exclusivity. As this exclusivity protects the product, rather than the submitted data, no generic applications will be accepted by the FDA during the five-year period, even if the applicant produces data independently. As the FDA takes an average of around 20 months to approve an ANDA following submission,<sup>44</sup> the effective exclusivity obtained in the US is usually over 6 years.

The US approach is a more favourable option for generics manufacturers, as these firms will usually wait for exclusivity to expire rather than reproducing test data, due to the expense and effort in doing so.<sup>45</sup> Therefore, the fact that the US offers complete market exclusivity is of little impact. The most important factor is that producers would rather wait for 5 years than 8 before being able to submit an ANDA. Innovative firms, knowing that generics producers will not reproduce test data, will naturally favour the European approach.

The US also offers an extended 7-year exclusivity period for orphan drugs,<sup>46</sup> to encourage research into treatments for rare diseases. These drugs do not usually make large profits, and therefore innovators may decide not to patent them, due to the expenses involved. An extended market exclusivity term will provide low-cost but effective protection, and provides an incentive for research in what are usually seen as high-risk, low-profit activities. Research into rare diseases also provides an indirect advantage for specialist clinics based in the US, which will be helped

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<sup>44</sup> [www.ranbaxy.com/inv\\_2004/investors\\_meet\\_2004.ppt](http://www.ranbaxy.com/inv_2004/investors_meet_2004.ppt)

<sup>45</sup> Interview with Marie-Therese Rainey, legal advisor in regulatory affairs and pharmacovigilance to the EMEA. *Managing Intellectual Property*, 82, 24-27

<sup>46</sup> Drugs used to treat 200000 people or less.

by the benefits of added research into such conditions, and any new treatments that may emerge as a result.

#### **4.2 Protection of new indications**

This is another field where EC and US legislation differ considerably. The EC only recently introduced legislation protecting new indications. This protection involves the extension of the data protection term for the original reference product by one year. The protection term for the new indication will be covered under the extended term for the reference product. The data protection term for the new indication will expire along with that for the reference NDA, and any subsequent ANDA will cover any new indications that are based on the relevant reference product.

This procedure is significantly different to that in the US, where each new indication receives an additional three years protection, independent of the original reference product.

The advantage with the US approach is that unlike the EC approach, it provides an incentive for continued research and improvement of existing treatments, as each new indication will be awarded its own period of exclusivity. The EC offers an incentive for the first new indication, but no additional incentive for subsequent improvements, as the one-year extensions are not cumulative. Although this approach does provide an incentive for post-approval research, there will be no incentive for continued research after the first new indication is approved.

The US approach also has its problems. As each new indication is protected for three years, the innovator can start a chain of improvements, known as a “Follow-on Product Strategy”.<sup>47</sup> This involves staggering applications for new indications, with each subsequent indication obtaining its own exclusivity period. This will leave generic competitors marketing products using outdated indications, while the originator’s version will use the latest indication. This will continue until the

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<sup>47</sup> CZABAN, J and LESKOVSEK, N., 2003. *Beyond the Patent Term: Regulatory Exclusivities In The U.S. Pharmaceutical Market - Crucial Issues and Strategies*. Available at: <http://www.hewm.com/use/articles/BeyondthePatentTerm.pdf>

innovator ceases to seek approval for new indications. Although this does not stop generic competition, the originator's product, which is usually branded, may be seen as more effective, and thus will not be as widely replaced with generic substitutes, allowing the originator to retain a large portion of the market share, thus raising costs for end consumers. It also promotes the commonly misconceived notion that generic drugs are less effective than those produced by the originator, a message the generics industry is keen to avoid. The problems caused by such a strategy are often intensified by the use of advertising.

This system of approval for new indications has led to generics firms using "carve out" strategies,<sup>48</sup> which involve omitting information on the packaging and labelling that could infringe the exclusivity offered to a protected indication. This is subject to the requirement that the safety of the drug is not compromised. Innovatory firms that obtain protection for new indications often respond with a strategy known as "discontinued labelling", whereby labels are continually revised to prevent the safe and legitimate use of "carve out" strategies.

The EC and the US have taken to rather extreme measures in respect of new indications. Some argue that European protection is inadequate,<sup>49</sup> while others believe the US system offers excessive protection for new indications. Many have accused the EC of favouring generics producers when it comes to new indications, especially following the outcomes of *Generics UK* and *Novartis*.<sup>50</sup> The new European one-year extensions are certainly a concession to these critics, but they have certainly not been appeased, and some are still pursuing stronger protection for new indications.

### **4.3 Marketing, Branding and TV Advertising**

Innovatory firms are known to use monopoly periods wisely, not only to ensure maximum profits during patent life, but also to develop brands for their products. These brands act as an assurance of quality, and firms will use these brands to

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<sup>48</sup> *Ibid*

<sup>49</sup> CAMPOLINI, M., 2004. "Fixing the Safety Net" *Patent World*, 2004, 162, 25-29

<sup>50</sup> JONES, N., and NITTENBERG, R., 1999. "Essentially Similar" despite being Different – the Squibb Case. *European Intellectual Property Review*. 21(4), 217-219.

retain as much of their market share as possible upon patent expiry. The advertising of branded prescription drugs is an interesting phenomenon that can have significant consequences for the industry. Most countries, including Canada and the members of the EC, have outlawed direct-to-consumer television advertising for prescription-only medicines. The main concern associated with such advertising is that it gives patients the impression that branded drugs are more effective than their generic counterparts. In countries with managed, state-funded healthcare such as the UK and Australia, patients are always subscribed generic drugs wherever possible. Allowing patients to be exposed to advertisements for drugs may lead to conflicts between doctors and patients, and may lead to unnecessary additional expenses for health services. However, in the US, healthcare is largely private, and advertising pharmaceuticals is common practice. This often leads to consumers demanding branded medicines at premium prices, and allowing innovatory firms to retain a significant share of the market after patent expiry. Coupled with the procedures for the protection of new indications in the US, this can make it difficult for generics producers to allay rumours of inferior performance, and thus make it more difficult for them to obtain a sizeable share of the market upon patent expiry. The advertising of new indications for branded drugs has also been used to significantly reduce demand for older indications that are used by generics manufacturers. Such a tactic was used by Eli-Lilly to encourage the use of a protected new indication of its popular antidepressant Prozac over generic substitutes of the original indication upon patent expiry.<sup>51</sup>

Another problem caused by advertising is that companies will spend large amounts of money on marketing existing brands rather than invest in R&D to produce new ones. It has been suggested that research based pharmaceutical firms often spend more on marketing existing brands than they do on R&D.<sup>52</sup>

The exception to the prohibition of television advertising in Europe and many other countries is with openly available “over-the-counter” drugs, where

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<sup>51</sup> WIRZ, M., 2003. Are Patents Really Limited to 20 Years? *Oklahoma Journal of Law & Technology*, Unknown.

<sup>52</sup> GLASGOW, L., 2001. Stretching the Limits of Intellectual Property Rights: Has the Pharmaceutical Industry Gone Too Far? *IDEA*, 227, 235-36

advertising is common practice, and where branded drugs often retain a sizeable portion of the market share after patent expiry. Advertising drugs in printed media is allowed in certain European countries, notably Germany and Switzerland.

#### **4.4 Approved Drug Products with Therapeutic Equivalence Evaluations - The “Orange Book” Rule.**

The “Orange Book” is a concept devised in the US, whereby NDA applicants are required to state the patents that they believe will be infringed by an ANDA that is approved before the patents expire. These patents are then quoted in a publication that states the patents that cover particular drugs. This is a useful measure for generic applicants that are considering ANDAs to determine which patents cover the drug in question and when they will expire. The “Orange Book” rule also benefits patent owners, as any applicant filing a Paragraph IV ANDA (see below) must notify the patent proprietor. ANDA applicants are also required to state their intentions with regard to each patent listed as relevant to the reference product. This saves patent owners the expense of employing “patent watching” services to notify them of potential infringements, and provides a minor entry barrier for generics firms. Some see the “Orange Book” rule as favouring originators and strengthening patent protection.<sup>53</sup> However, it works in favour of both innovators and generics firms, helping the latter to plan ahead, providing information on patents and reducing the risk of unexpected patent infringements, and helping patent owners to detect infringements without relying on expensive watching services.

#### **4.5 Paragraph IV ANDA Applications in the US**

The US divides ANDAs into four main categories:<sup>54</sup>

- (1) that patent information on the drug has not been filed;
- (2) that the patent has already expired;

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<sup>53</sup> KAMATH, G, 2003. *Drug Patents: The Linkage Issue*. BusinessWorld India. Available at: <http://www.businessworldindia.com/Dec1503/news06.asp>

<sup>54</sup> SCHACHT, W.H. and THOMAS, J.R. (2003) *The Hatch-Waxman Act: Proposed Legislative Changes Affecting Pharmaceutical Patents* [online]. Congressional Research Service. Available from [http://www.ipmall.info/hosted\\_resources/crs/IB10105.pdf](http://www.ipmall.info/hosted_resources/crs/IB10105.pdf)

- (3) the date on which the patent will expire; or
- (4) that the patent is invalid or will not be infringed by the manufacture, use or sale of the drug for which the ANDA is submitted.”

The first two would mean that the ANDA would be authorised upon the expiry of any market exclusivity under Hatch-Waxman, and the third from the date of the expiry of either the patent or the exclusivity period, whichever is the later.

The fourth is a form of ANDA not available in Europe, and largely made possible by the US Orange Book concept. It is effectively a contentious generic application, known as a Paragraph IV application, which is filed together with a claim that the originator’s “Orange book” patent(s) are invalid or not infringed by the generic. The first applicant to file a Paragraph IV ANDA is rewarded with 180 days market exclusivity following authorisation. This effectively encourages generic applicants to challenge the validity of patents and the scope of patent claims. Patent owners naturally have the tendency to argue the validity and scope of their patents, and usually counterclaim for patent infringement. In such cases, the ANDA is suspended until the patent is declared invalid, up to a maximum suspension of 30 months. If a patent is found to be valid and infringed by the generic, the ANDA will not be approved until the patent expires. Following the outcome of *Mova Pharmaceutical Corp. v. Shalala*, the 180-day exclusivity period will be awarded to the Para. IV applicant even if their defence against a patent infringement suit is unsuccessful, and the ANDA is not approved until after patent expiry. The existence of this procedure partly explains the relatively large volume of patent revocation suits in the US. The Paragraph IV procedure provides an avenue for generics manufacturers to find and attack weak patents, and gain quick access to markets using an integrated revocation and ANDA procedure, rather than waiting for patents to expire. It is estimated that in 2002, 70% of Para. IV ANDAs were successful,<sup>55</sup> indicating that the procedure is of benefit to generics manufacturers.

In Europe, no such procedure exists, which means that applicants who wish to invalidate a patent in order to release a generic onto the market will have to file

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<sup>55</sup> Navigant Consulting, 2004. *Generic Pharmaceutical Litigation*. Available from: <http://www.navigantconsulting.com/lifesciences/SMR/genlit/genlitSP.pdf>

invalidation proceedings and ANDAs separately. However, even if such a patent revocation action is successful, originators will often still be protected by the lengthy data exclusivity terms offered in Europe, which means that it is cheaper and less risky for generics firms to wait for patent expiry before launching a generic product, thus explaining the relatively low volume of revocation actions in Europe in comparison to the US.

#### **4.6 “Evergreen” Patents**

Under US law, any ANDA that becomes the subject of a patent infringement claim is given a stay of a maximum of 30 months under the Hatch-Waxman Act, delaying the approval of that generic until the expiry of this period, or until a court decision acquits the generics firm from any wrongdoing. This procedure has become the victim of much abuse by pharmaceutical companies.<sup>56</sup>

As market exclusivity for drugs is often worth millions of dollars a day, pharmaceutical companies have often used a strategy known as “evergreening” to extend their monopoly beyond patent expiry. This strategy involves issuing patent infringement proceedings against ANDA applicants just before a patent is due to expire. This triggers the automatic 30-month stay for the ANDAs, allowing the originator to effectively retain its monopoly for 30 months following patent expiry. This 30-month stay is often confused with PTEs under Hatch-Waxman, although they are separate, unrelated procedures. This strategy has been the cause of several frivolous patent infringement claims, which are designed solely to trigger the 30-month stay and have no legal basis.

Companies that market products covered by several patents have often triggered progressive delays for ANDAs by filing multiple, staggered infringement proceedings based on different patents. The US Government has since closed this loophole by only allowing one delay per product.<sup>57</sup>

The legislative loophole that allowed evergreening has drawn much criticism to the Hatch-Waxman act, and is often seen as the major failing of an otherwise extremely successful and popular bill. It has also been proposed that legislation be

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<sup>56</sup> JOSEFSON, D., 2002 US Senate considers proposal to tighten drug patent law, *British Medical Journal*, 324, 1176.

<sup>57</sup> BBC News, 2002. *US Plans boost for generic drugs*. Available From: <http://news.bbc.co.uk/2/hi/business/2348185.stm>

amended to eliminate the automatic 30 month stay, and that any delays in ANDA proceedings should be determined by a court on a case-by-case basis.<sup>58</sup>

Europe does not automatically delay ANDAs when proceedings are issued against the applicant, therefore this issue is not encountered.

#### **4.7 Exclusivity Periods for Generics**

Under certain circumstances, the first generics firm to enter the market will be awarded a 180-day exclusivity period. This is notably the case for Para. IV applicants. Although this allows a generic competitor to gain an advantage by seizing a significant portion of the market share before others enter the market, it has also been used to the advantage of innovatory firms. These firms have been known to pay generics firms not to market their products during the 180 day period, effectively giving the originator another half a year of market exclusivity.<sup>59</sup> This has since been changed such that if the first ANDA applicant does not market their product within 75 days of approval,<sup>60</sup> the 180-day exclusivity period will be nullified. However, due to the high value of market exclusivity, originators still have an incentive to carry on this practice, as even 70 days of exclusivity can be worth millions of dollars.

Europe has managed to avoid controversy in this area as it does not offer any exclusivity period to generic applicants, thus often resulting in several generic competitors entering the market at the same time, making it difficult for originators to reach deals preventing competition.

#### **4.8 Europe's Single Trade Mark Rule**

A major economic advantage the US has over Europe is that it is a single market. Europe, in a move to encourage the Community to behave as a single market, requires any applications for Community marketing authorisations through the EMEA to specify a single trade mark that the drug will be marketed under. This

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<sup>58</sup> ROSENTHAL, J., 2002. Hatch-Waxman Use or Abuse? Collusive Settlements Between Brand-Name and Generic Drug Manufacturers, *Berkeley Tech. Law Journal*, 17 (317), 328-29.

<sup>59</sup> GLASGOW, L., 2001. Stretching the Limits of Intellectual Property Rights: Has the Pharmaceutical Industry Gone Too Far? *IDEA*, 227, 235-36.

<sup>60</sup> Navigant Consulting, 2004. *Generic Pharmaceutical Litigation*. Available from: <http://www.navigantconsulting.com/lifesciences/SMR/genlit/genlitSP.pdf>

encourages the free movement of goods throughout the community. This means that, for example, the UK's NHS will be able to source a drug from Poland if prices are lower. This makes it difficult for manufacturers to fix prices in individual countries. From a marketing point of view, using a single trade mark across Europe is easier, as brands will be recognised by people from across the continent. It is also a step towards global branding, as a single European brand is likely to bear similarities to its counterparts in the US and other major markets. However, despite its numerous advantages, the compulsory requirement for a single trade-mark has come under criticism for being an unnecessary complication that reduces flexibility and disadvantages firms.<sup>61</sup>

#### **4.9 Second Medicinal Uses – Swiss-Type Claims**

Second medicinal use claims,<sup>62</sup> involve formulating patent claims to protect the use of a drug in treating a condition other than that it was originally designed for. Such claims usually take the form of "The use of (substance X) in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of (medical condition Y)".<sup>63</sup> Such claims require some evidence, and although detailed clinical studies are not required, purely speculative claims will not be accepted.<sup>64</sup> A UK court decided in *American Home Products Corp. v Novartis Pharmaceuticals UK Ltd.*<sup>65</sup> that derivatives of the patented product(s) would not be covered by second medicinal use claims, as it could not be proven that all derivatives would be effective for the claimed purpose, and therefore any claim relating to derivatives did not provide sufficient information for a skilled person to determine which derivatives would work and to formulate an effective treatment.

Swiss-type claims do not protect new indications, as this involved detailing new information regarding the first medicinal use, rather than a new medicinal use that is different from the originally intended purpose.<sup>66</sup>

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<sup>61</sup> ROBINS, A., 2002. Making Europe's pharma industry competitive. *Managing Intellectual Property*, 124, 5

<sup>62</sup> Known as Swiss-type claims as they were first accepted by the Swiss Patent Office.

<sup>63</sup> Examination Guidelines for Patent Applications relating to Medical Inventions in the UK Patent Office (March 2004). Available from:

<http://www.patent.gov.uk/patent/reference/mediguilines/second.htm>

<sup>64</sup> Prendergast's Applications [2000] RPC 446

<sup>65</sup> [2001] RPC 159

<sup>66</sup> Bristol-Myers Squibb Co. v Baker Norton Pharmaceuticals Inc. [2001] RPC 1

Some countries have been more willing to accept such claims than others. The US has been keen to accept these claims, but European countries, notably the UK, have been more reluctant, and have only done so with certain restrictions applying.

## **5. Data Exclusivity and TRIPS**

The protection of test data is covered under Article 39.3 of TRIPS. This does not provide detailed information as to what is required of data protection measures, allowing considerable flexibility for countries that are yet to introduce legislation. The minimum standard of data protection required by TRIPS is much weaker than that available under US or European legislation mentioned earlier. There are certain criteria, however, that need to be met.

Firstly, only data that is required as part of an application is required to be protected. Therefore, the protection of supporting data that is surplus to the requirements of the application procedure need not be protected. Any protection afforded to such supporting data will be supplementary to the requirements of TRIPS. Such “TRIPS-plus” measures have often been criticised by certain development organisations as such measures offer stronger intellectual property protection than required by international law, advantaging innovatory firms over generics manufacturers.

Secondly, only data submitted regarding the approval of a new chemical entity is covered under Art. 39.3. This means that new indications of existing treatments do not need to be covered. New uses of existing treatments are also excluded from Art. 39.3. The definition of “new chemical entity” is again open to interpretation. If incorporated into legislation, the scope of the definition will have a major impact on the ambit of protection offered under that legislation.

Thirdly, protection shall only be awarded when the data produced are the result of “considerable effort”. This is in line with the argument that data protection is a reward for effort rather than innovation.<sup>67</sup> Legislation in the developed world has tended towards protecting all data submitted as part of NDAs, without the need to prove “considerable effort”. It will again be the decision of individual countries to decide whether this test is necessary.

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<sup>67</sup> Correa, C.M. (2002). *Protection of Data Submitted for the Registration of Pharmaceuticals: Implementing the Standards of the Trips Agreement* [online]. Geneva, The South Centre. (“Correa”). Available from: <http://www.southcentre.org/publications/protection/protection.pdf>

Finally, data must be protected from “unfair commercial use”. The ambit of this term is again subject to manipulation, depending on the definition of the individual terms. The “unfairness” test is particularly flexible, but one that could lead to legal action from developed countries if the standard of protection is deemed inadequate. There is no relevant case law that defines “unfair” in this context, although *Correa* provides some clarification by studying the law of unfair competition in the context of the Paris Convention.

One of the flexibilities afforded to countries is the option to protect data through either confidentiality, or through a *sui generis* system of exclusivity provision as used in most developed countries.

A discussion of the options available to developing countries is detailed later in this study.

## **6. Differences between Markets and Industries in Developed and Developing Countries.**

Intellectual property legislation is relatively new to most developing countries, and recommendations for legislative measures cannot be based on the successes and failings of IP measures in developed countries alone. The nature of markets and practices in developing countries must be taken into account.

India is a good example of a developing country with a flourishing pharmaceutical industry, but which still faces major problems in overcoming poverty and disease. India currently has one of the largest generics industries in the world. Of the \$27bn worldwide generics market in 2001, Indian firms accounted for around \$7bn. By 2007, the market will have a projected value of \$57bn, with Indian firms projected to account for over a third.<sup>68</sup> India has the capacity to produce drugs for a large number of LDCs without such production capacities. Legislation in India will therefore have an indirect effect on the supply of generic drugs throughout the developing world. So far, India has resisted pressure from the developed world to introduce strong intellectual property measures in excess of those required under TRIPS. However, its decisions will be of significant importance to its public health measures and to the development of the global generics market.

Currently, the most important issue for India is increasing the availability of effective, affordable drugs to deal the country's mounting public health problems. As there is little state healthcare available, most people, many of whom live below the poverty line, are forced to pay for their own treatments. As such, the Indian market requires large quantities of low cost drugs to treat disease, many of which are unique to the region, together with globally problematic diseases such as malaria and AIDS.

Unfortunately, the bulk of pharmaceutical research carried out by multinationals is directed at problems faced in the developed world, as successful treatments can obtain patent protection and investment can be recovered. The same does not

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<sup>68</sup> JISHNU, L. (2004) *The cost of protecting data*. BusinessWorld India. Available at: <http://www.businessworldindia.com/Jan2604/indepth01.asp>  
Statistics provided by Datamonitor UK.

apply to developing countries. Research into diseases commonly encountered in these countries is considerable, but many multinationals are reluctant to engage in such research, as successful products are often copied by local generics firms due to the lack of effective patent legislation.<sup>69</sup> Countries such as India will either need to provide adequate protection for these multinationals to recover their investments, or rely on its own industries to develop treatments.

India is one of the more fortunate developing countries with regards to medicines, as its home-grown generic pharmaceuticals industry has expanded rapidly in recent years, with firms such as Dr. Reddy's, Cipla and Ranbaxy now having a global presence. These firms are now large enough to invest in R&D and develop their own drugs.<sup>70</sup> This provides a useful resource in dealing with local health problems. Other smaller firms, until recently, have still focused on retrosynthesising drugs and producing their own generic variants through different processes, which was legal in India until transitional legislation was introduced, allowing product patents.

Legislation should take into account the needs of local firms. One of the objectives of TRIPS was to allow developing countries to foster their own innovative industries. As seen in India, successful local generics firms have developed into multinationals that are increasingly focusing on innovation. Such growth and development should be encouraged to reduce dependence on drugs originating from firms based in developed countries, and as such legislation should not stifle the activities of smaller generics firms, allowing them to grow and eventually develop their own research capacity.

Patent legislation covering products for 20 years will be introduced in India in January 2005. This will inevitably result in foreign and local firms filing patents on their products, which will restrict the production of generic versions of patented products. According to *Barracough*, it is expected that patent legislation will not significantly exceed the requirements of TRIPS.

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<sup>69</sup> BARRACLOUGH, E., 2004. Industry fears drugs law reversal. *Managing Intellectual Property*, 141, 17-20

<sup>70</sup> Ranbaxy Laboratories Ltd. Investors Meeting, 9 September 2004, Mumbai. [www.ranbaxy.com/inv\\_2004/investors\\_meet\\_2004.ppt](http://www.ranbaxy.com/inv_2004/investors_meet_2004.ppt)

The goals of any TRIPS compliant patent and data protection legislation in India will include ensuring the best possible levels of availability of cheap drugs to treat the most common local diseases. Legislation should also provide adequate protection to the R&D investments of local firms such as Ranbaxy by providing adequate intellectual property protection, without stifling generic drug production that local firms thrive on.

The transition from patent monopolies to free markets will have a significant influence on the generics industry, as any delays or entry barriers following patent expiry will discourage generics firms from entering the market. Legislation should therefore allow the introduction of generic competition as quickly and cheaply as possible following patent expiry. In addition, it should encourage the entry of multiple generic competitors. A Canadian study<sup>71</sup> has shown that the price of generic substitutes falls steadily with the number of competitors, until around five competitors are in the market. Therefore, legislation that encourages multiple competitors to enter the market will be more effective at lowering prices.

An important provision available to India and other developing countries is the use of compulsory licensing. Any additional protection measures, especially data exclusivity, should ensure that it does not interfere with compulsory licensing measures, as this will limit the effectiveness of such a measure in dealing with public health emergencies.

Another characteristic of the Indian medicines market is the heavy presence of herbal medicines. These will not be protected by patents, and therefore any protection afforded to them will be through data protection. In deciding whether to protect these, policymakers must consider whether any protection afforded to herbal medicines will benefit public health and local industry.

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<sup>71</sup> LEXCHIN, J. (2004) *Brief to the Industry, Science and Technology Committee on Bill C-9, An Act to Amend the Patent Act and the Food and Drugs Act*. Available at: [http://www.aidslaw.ca/Maincontent/issues/cts/patent-amend/submissions%200304/Bill%20C-9\\_Lexchin%20Brief\\_Feb%202004.PDF](http://www.aidslaw.ca/Maincontent/issues/cts/patent-amend/submissions%200304/Bill%20C-9_Lexchin%20Brief_Feb%202004.PDF)

Black market medicine is a growing problem in India and other developing countries.<sup>72</sup> Such medicine is often the result of high drug prices, forcing poorer patients to take a chance with illegally produced copies. These are usually produced by organised criminals and are often unsafe. A problem caused by TRIPS is that smaller generics firms that have previously been able to sidestep patent legislation may be forced out of legitimate business, and some may resort to producing drugs illegally, causing a boom in the black market. Legislation must ensure that these companies are given a chance to stay in legitimate business.

A large proportion of drugs that will be patented and submitted for approval in India will not have been developed in India, nor have been developed specifically for the Indian market.<sup>73</sup> Therefore, patent and marketing authorisation applications will often be based on those submitted in developed countries. Procedures will need to take this into account if they are to ensure maximum efficiency in processing applications.

Finally, it is important to note that regulatory bodies will not have access to the same degree of funding as their counterparts in developed countries. Therefore, it must be taken into account that applications will usually take longer to process, and allowances must be made for this, as long delays could hold up generic entry and give unfair advantages to patent holders.

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<sup>72</sup> BBC World Service. Black Market Medicines. Available at:  
[http://www.bbc.co.uk/worldservice/specials/1718\\_pills/page4.shtml](http://www.bbc.co.uk/worldservice/specials/1718_pills/page4.shtml)

<sup>73</sup> "Only 1% of drugs developed in the last 25 years have been to treat illnesses of developing countries." [http://www.bbc.co.uk/worldservice/specials/1718\\_pills/index.shtml](http://www.bbc.co.uk/worldservice/specials/1718_pills/index.shtml)

## **7. Recommendations for Developing Countries in Respect of the Transition from Patent Protection to Free Markets.**

Following detailed study of the concepts considered in the development of legislation in the developed world, together with a knowledge of market conditions in developing countries, it is possible to recommend legislative concepts that would work in favour of developing economies. Such concepts must be within the boundaries of the TRIPS agreement, the wording and interpretation of which will be very important in selecting and modifying concepts to be used.

The suggestions made in this section are designed primarily for countries that already have the capacity to produce pharmaceuticals, and focus largely on enacting legislation that will encourage the growth and development of local industries, usually focusing on generics, rather than providing strong TRIPS-plus protection to encourage foreign investment. The reason for this is that local public health provisions rely on generic drugs, and to encourage foreign investment at the expense of generics and public health measures would be ethically questionable. In addition, one of the reasons for TRIPS, as mentioned earlier, was to enable countries to develop their own innovative industries. Indian firms have shown that successful generics businesses can grow into multinational companies with a considerable research capacity. Thus, these recommendations will focus on encouraging maximum generic competition upon the transition to a free market and encouraging the growth and development of local industries, whilst seeking to protect intellectual property rights as required under TRIPS.

### **7.1 Regulatory Data Protection**

It is likely that developing countries will adopt some form of regulatory system, if they haven't already done so. To refrain from adequately regulating drugs would compromise the safety of medical treatment available in the country, putting citizens at risk from inadequately tested, poorly formulated medicines. Such regulatory systems should ensure that all drugs authorised for use in a country are safe and effective for the intended purpose. As such, any data submitted as part of

applications for regulatory approval will need to be protected, as required under Art. 39.3 of TRIPS.

An effective regulatory system will require data from exhaustive tests before a new drug is approved for use. There are two ways of protecting such data, either through confidentiality or offering a limited period of exclusivity.

Providing confidentiality for test data is a simple provision that would prevent authorities from disclosing test data, meaning that it cannot be accessed by competitors. However, the measure does not protect the originator from ANDA applications that refer to the data. In the UK, the House of Lords decided in *R. v Licensing Authority Ex p. Smith Kline & French Laboratories Ltd (No.1)*<sup>74</sup> that regulatory authorities were permitted to refer to confidential data when approving generic competition. This was advantageous for generic competitors, as they could submit ANDAs for approval immediately after the originator is granted marketing authorisation.

Although confidentiality could work in favour of generics, the enforcement of such a measure is extremely difficult due to the free movement of information. As data exclusivity is offered in most developed countries, manufacturers in these countries will tend to publish the data in journals, knowing that it cannot be used by a competitor. Confidentiality would therefore offer little protection to data in developing countries, as potential competitors could simply gain access to a foreign journal and obtain the data. This may have global repercussions, as manufacturers may become reluctant to publish data in developed countries, knowing that it can be copied in developing countries without exclusivity provisions. Publication of data is important, as it allows medical practitioners to better understand the functions and dynamics of the drug.<sup>75</sup> Discouraging such publications could limit information available to doctors, which would be detrimental to public health in the country concerned as well as globally, and therefore confidentiality would not be a desirable measure in the context of improving public health.

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<sup>74</sup> [1990] 1 A.C. 64

<sup>75</sup> OLLILA, E, HEMMINKI, E. 1996. Secrecy in drug regulation. *Int J Risk Safety Med*, 9, 161-72.

Exclusivity of data, although unpopular with many developing countries, is a more favourable option, as it is easier to enforce, and will not disadvantage public health by discouraging the publication of data. However, it must be carefully decided what should be protected, and the extent to which it should be protected, as excessive protection will adversely affect generic introduction.

## **7.2 Definition of “New Chemical Entity”, and the Protection of Herbal Medicines.**

TRIPS only requires the protection of “new chemical entities”. Anything surpassing this requirement will be TRIPS-plus and at the discretion of the country concerned. In considering whether to restrict exclusivity to NCEs, an issue that countries will have to address is whether they wish to use regulatory data provisions as a “safety net” by providing protection for unpatentable inventions. Such protection would offer security to local research in case inventions cannot be patented. However, it will also allow foreign firms to seek data exclusivity for unpatentable inventions, thus delaying the introduction of generic variants of unpatented medicines. As the majority of local firms rely on being able to produce generics, it seems that protection should be restricted to NCEs as required under TRIPS, as additional protection will be contrary to public health requirements and the development needs of local industry.

A problem with this is that it does not reduce risk for local companies with growing R&D capacities that are developing drugs to combat local health issues. However, incentives to carry out such research can easily be provided by other means, such as tax breaks, and therefore data exclusivity beyond NCEs is not strictly necessary in promoting innovation. If data exclusivity is restricted to NCEs, alternative incentives should be provided to prevent firms moving research facilities to countries with stronger protection measures.

An important factor affecting the scope of protection afforded by data exclusivity will be the definition of “new chemical entity”. Two examples are as follows:

IUPAC<sup>76</sup> defines “new chemical entity” as “a compound not previously described in the literature”. Another definition suggested by *Correa* interprets “new” as requiring a patent standard of novelty.

Using the IUPAC definition will protect compounds “not previously described in the literature”. This notably does not cover “traditional knowledge”, which means that previously unresearched traditional herbal and naturally derived treatments will be eligible for protection if their safety and efficacy can be demonstrated. This will encourage firms to research, test and market such remedies, resulting in herbal remedies with scientifically proven therapeutic characteristics potentially being developed into pharmaceutical products. Traditional herbal medicines are commonly used in developing countries, and although some are effective, others are merely placebos. Such remedies are an important resource for developing countries, with the potential for worldwide marketing if they are researched and developed successfully. They are also the subject of traditional knowledge, and allowing pharmaceutical firms to exploit and profiteer from such knowledge would be inequitable.

Offering exclusivity for such products will result in higher prices for the exclusivity period, which may result in many poorer people being deprived of traditional remedies they often rely on. In addition, it may encourage biopiracy,<sup>77</sup> with firms profiteering by seeking protection for successful traditional medicines.

Thus, if naturally occurring substances are to be covered under the ambit of “new chemical entity”, data exclusivity regulations should ensure that effective natural substances can obtain data exclusivity without depriving people of traditionally produced variants of the remedy. Exclusivity should thus be restricted to the use of test data, without following US practice and offering complete market exclusivity. A “prior use” provision should allow the continued use and sale of safe, traditionally produced medicines without approval, whilst pharmaceutical grade indications of the active substance will require approval for marketing. In

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<sup>76</sup> International Union of Pure and Applied Chemistry

<sup>77</sup> DRAHOS, P., 2000. Indigenous Knowledge, Intellectual Property and Biopiracy: Is a Global Bio-collecting Society the answer? *European Intellectual Property Review*, 22(6), 245-250

addition, countries that choose to protect pharmaceuticals based on traditional remedies will need to adopt strict controls to control bioprospecting activities to prevent biopiracy and other forms of unethical exploitation of traditional knowledge.

*Correa's* suggestion for the definition of “new chemical entity” would define “new” as requiring a standard of novelty as required under patent legislation. This definition is conceptually similar to IUPAC’s, as “novel” by patent standards is defined as “not part of the prior art”. The main difference between this definition and the IUPAC definition is that “prior art” covers all previous public knowledge, regardless of whether it has been published. The notable exception that leads to is the lack of protection for natural compounds that have been used traditionally but never documented, as traditional knowledge will form part of the prior art. Traditional medicines are ineligible from patent protection in many countries for the same reason. Incorporating the novelty standard into data exclusivity provisions would mean that certain unpatentable products and drugs based on traditional remedies that obtain approval would not receive data exclusivity, and will immediately be vulnerable to the granting of ANDAs for generic competitors shortly after approval. Although this lack of protection would discourage biopiracy, it would stifle any research into traditional medicines, which countries that are rich in biological resources may view as an important channel towards developing unique, locally sourced and produced products that can be sold internationally.

Another advantage to generics manufacturers of the requirement of novelty for NCEs is in patent litigation. If a patent is invalidated on grounds of novelty, then by definition that compound is also not a new chemical entity, and therefore any data exclusivity protecting it can lawfully be revoked, allowing the invalidator to bring out a generic immediately upon such an invalidation, rather than having to wait for the data exclusivity to expire.

An important consideration indicated by *Correa* when defining “new chemical entity” is whether “new” is to be considered in a universal or local context.<sup>78</sup> Defining it in a local context will allow protection for substances that are new in the country concerned, even if they have already been in established use outside that country. This is not desirable, as it will allow firms to stall in making a drug available in a country, and thus delaying the availability of an important drug, any eventual generic competition.

Defining “new” in a universal context will mean that applications for a new drug will have to be submitted before a drug is launched, as once it is launched in one country, it is no longer “new”, and thus not eligible for data protection in countries that have an NCE requirement for data exclusivity. This will encourage the synchronisation of approvals in developing countries with those in developed nations, as well as denying protection to old but previously unapproved drugs, allowing generic variants of such drugs to be produced if required.

In summary, the definition of “new chemical entity” provides a degree of flexibility. In defining this term, countries will have to take into consideration whether they wish to offer protection for NDA data relating to traditional remedies, providing incentives to research and test such medicines and to develop effective products from them. Countries that allow exclusivity for drugs based on traditional remedies should ensure that such measures do not affect the traditional production of these medicines, and that adequate measures are in place to prevent biopiracy, possibly through the regulation of bioprospecting. As data exclusivity periods are generally much shorter than patents, using this measure to protect natural products will encourage research without resulting in lengthy monopolies. The “newness” of an NCE should also be defined universally, in order to prevent any undue stalling of applications for authorisation.

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<sup>78</sup> CORREA, C.M. (2002). *Protection of Data Submitted for the Registration of Pharmaceuticals: Implementing the Standards of the Trips Agreement* [online]. Geneva, The South Centre. Available from: <http://www.southcentre.org/publications/protection/protection.pdf>

### **7.3 Mechanisms of Data Protection.**

Article 39.3 of TRIPS requires the prevention of “unfair commercial use” of test data. The definition of “unfair commercial use” is open to interpretation and provides considerable flexibility in the enactment of legislation. There is no official clarification regarding the exact meaning of the term, and little case law that details the possibilities available under this provision. A detailed dissection of the term is available in *Correa*.

One of the goals of data protection legislation in developing countries is to ensure the swift introduction of an optimal level of generic competition upon expiry, resulting in the lowest possible prices. This is achieved by encouraging the introduction of multiple generic competitors. Legislation should therefore ensure that entry barriers for generics firms are as low as possible, thus encouraging them to enter the market due to the low associated costs.

A successful means of doing this is by allowing ANDAs, therefore relieving generics firms of the burden of having to repeat expensive tests and trials, which is the most considerable entry barrier they could face in entering the market. ANDA provisions alone would be in violation of TRIPS, but providing a limited data exclusivity period before ANDAs are approved is seen as a legitimate solution, as it is common practice in most developed countries. This approach lowers entry barriers for generics whilst providing adequate protection for originators as required by TRIPS. The shortest exclusivity period is that of the US, which is five years. This is an adequate term for developing countries to follow, as any shorter terms may draw international criticism.

In the US, the submission of ANDAs is not permitted during the exclusivity period, resulting in a longer effective exclusivity. If effective exclusivity is not to exceed the five-year protection period, a country will need to allow the submission of ANDAs during the exclusivity period, as practiced in Europe. This will rely on the presence of Bolar provisions that allow generics manufacturers to conduct the relevant bioavailability testing before patent expiry. Authorities will require enough time to approve the application. The FDA takes around 20 months, but

regulatory agencies in developing countries are unlikely to receive the same degree of funding, and so may take longer. As this is the case, ANDA applications should be permitted at any time following the original authorisation, providing they are not approved until the expiry of the exclusivity period and relevant patents.

Under such provisions, if regulatory authorities can ensure that a marketing authorisation is made within the first 15 years of the corresponding patent's life, a generic variant can be authorised using the ANDA procedure immediately upon patent expiry, thus resulting in the introduction of generics onto the market shortly after patent expiry.

However, as NDAs can often be delayed, exclusivity periods may extend beyond patent expiry. The use of patent linkages in the EC has long been a solution to this, although it is no longer used, as it was decided that such a provision may be in violation of TRIPS.<sup>79</sup> Although this would be a useful solution for developing countries to prevent originators' monopolies extending beyond patent expiry, countries that decide to use this provision by default may face legal action from developed countries. The reasons given by *Cook* as to the illegality of such provisions is that automatic patent linkages would mean that products that are not covered by a patent will not be eligible for data protection at all, which is in violation of TRIPS, as this does not prevent "unfair commercial use" for data relating to unpatented products. A solution to this is to only allow patent linkages in cases where any delay in marketing authorisation is attributable to the applicant (e.g: through lack of due diligence), and that such linkages are not applicable to products that are not protected by patents. Linkages can also be applied to patents that are revoked, allowing rapid generic introduction following such cases.

#### **7.4 Summary Applications and the "Considerable Effort" Test**

Certain developing countries have already developed "summary application" procedures that permit drugs to be authorised on the basis that they are already

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<sup>79</sup> COOK, T., 2003. Regulatory Data Protection of Medicinal Products in Europe. *Bio-Science Law Review*, Unknown.

authorised abroad.<sup>80</sup> This saves both regulatory agencies and applicants time. Such procedures are mainly used by foreign applicants looking to authorise their products in several countries. If a country decided to implement summary application procedures, the information required by such applications will have an indirect effect on generics procedures.

As detailed in *Barreda*, Peru has a procedure which requires a simple proof of prior authorisation elsewhere. No data or other information is required. As such, the product is not protected in any way through such an application, as there is no data to protect, and therefore no protection is required under TRIPS. Therefore, if such a provision is present in legislation, any generic applicant will be eligible to apply for an ANDA immediately following a summary application, providing they can meet the criteria. In the absence of patent protection, the drug authorised through the summary procedure will be immediately vulnerable to generic competition.

This brings the demand for such a procedure into question. Applicants may opt to use the standard NDA procedure and be afforded exclusivity for their data, rather than using a summary procedure. As the data will have already been produced, there will not be much additional effort required to use the NDA procedure. This, however, brings into question the “Considerable Effort” test stipulated under TRIPS. Under Art. 39.3, data must only be protected if it is the result of considerable effort. It does not specify whether “effort” includes financial expenditure. Nor does it specify whether that “effort” is meant in a general perspective, or specifically in relation to the application in question. This is noteworthy, as in a case where an applicant has already applied for an NDA abroad, it is arguable whether the data can be considered the result of “considerable effort” in subsequent applications, as that effort was made primarily in order to obtain authorisation elsewhere. One test that could be used is whether that data would have been produced if protection were not available in the country concerned. In the case of most developing countries, the answer would be negative, as data would have been produced regardless, in order to obtain authorisation in developed countries. Therefore, developing countries can enact a

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<sup>80</sup> BARREDA, J., 2003. Protection of Data in the Pharmaceutical Sector. *Patent World*, December 2003. Unknown.

provision based on the “considerable effort” test whereby data that would have been produced at any rate is not entitled to protection, which is a major concession to generics manufacturers.

### **7.5 Data Protection and Compulsory Licensing**

Compulsory licensing is a measure that has been hailed as a lifeline for developing countries by many development organisations, as it allows the state to award a license to a generic manufacturer to produce a generic variant of a patented drug in the case of a public health emergency. This presents a danger to patent holders, as they risk having their patents undermined if such a procedure is used. In reality, such procedures are rarely used, due to the threat of recriminations from the international community, especially following the incidents regarding the compulsory licensing of AIDS drugs in South Africa and Brazil.<sup>81</sup> However, the threat of compulsory licensing is usually sufficiently effective in encouraging patent holders to keep prices affordable to a large proportion of a population.

Compulsory licensing measures are an effective means of keeping prices low and producing large quantities of cheap drugs when necessary. Data protection should therefore not interfere with such measures. Upon issuing a compulsory license, any data relating to the drug should be available to use by the state in producing the required drug, regardless of exclusivity. Continuing to enforce exclusivity during a compulsory license would undermine the effectiveness of the procedure. In addition, as compulsory licensing must be used by the state to treat public health emergencies, it is unlikely that the use of the data can be regarded as “commercial use”, and therefore such an exception would be legal under TRIPS.

### **7.6 New Indications and Extensions of Data Exclusivity Periods.**

Data exclusivity periods can obtain extensions in certain circumstances in developed countries. Such extensions are afforded in the case of new indications in Europe, and in the case of orphan drugs in the US. As the main health concerns of developing countries will revolve around dealing with major diseases such as

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<sup>81</sup> Canadian HIV/AIDS Legal Network, 2001. *Victory in South Africa, but the Struggle Continues*. Available at: <http://www.aidslaw.ca/Maincontent/issues/cts/updateSA.htm>

AIDS and malaria, rare diseases will not usually be a high priority, and therefore extended protection for these will be unnecessary in most cases.

The protection of new indications is not required by TRIPS, as these are not new chemical entities. However, continued research into authorised drugs is important, and although it is a TRIPS-plus measure, such a measure will offer distinct advantages to developing countries. Providing protection for new indications of a drug that are of “significant clinical benefit” to the local population could prove beneficial in encouraging firms to develop indications that are specific to local needs. As extended protection periods for new indications need not be long (1 year in Europe), the long-term gains from having indications that are tailored to a country’s needs will outweigh the losses due to high prices in the short term. Therefore, a short extension of data exclusivity periods for new indications could have lasting benefits. The definition of “significant clinical benefit” will have to be considered carefully to ensure that any new indications are beneficial to public health, and that firms do not submit applications for indications of limited benefit solely to obtain extended protection. Extensions for new indications should not be cumulative, as this will disadvantage generics through the possibility of “follow-on product” strategies as seen in the US.

### **7.7 Eligibility for ANDA Procedures**

Legislation must make the criteria for eligibility for abbreviated approvals clear and transparent. It is obvious that any generic drug must be bioequivalent to the original. In addition, the drug should have the same active substance(s), and its pharmaceutical form should not adversely affect its efficacy in relation to the original. As such, the European definition of “essential similarity” is a useful test for developing countries to use. The definition of “essentially similar” in *Generics UK* and *Novartis* was criticised for favouring generics producers. As this would be advantageous to such industries in developing countries, such a term would be a useful addition to legislation. European case law provides detailed clarification of the term, which can be a useful reference for developing countries in considering the eligibility of ANDA applications. The European definition also allows a degree of flexibility for developing countries to formulate their own definition,

unlike the US definition, which states that a generic has to be “the same as a listed drug”.

Europe also grants ANDA applicants authorisation to use any new indications within the ambit of “essential similarity”. This should also be allowed in developing countries, as it allows generics manufacturers to market the latest products, and eliminates any discrepancies between generic and originator drugs as experienced in the US.

### **7.8 Patent Listings**

Patent listing systems, such as the “Orange Book” in the US, although regarded as TRIPS-plus, can provide many benefits to developing countries. It allows regulatory authorities and potential applicants to easily determine if an ANDA will infringe a patent before the application is submitted. This prevents firms inadvertently infringing patents and facing expensive litigation.

This concept will also allow the enactment of a provision similar to Paragraph IV in the US allowing contentious ANDA applications. Such a provision will encourage local generics firms to challenge the validity of existing patents, and thus offer the chance of bringing generic variants onto the market before the relevant patent(s) are due to expire, which will lower prices and benefit public health.. Such a provision will also discourage the filing of weak or frivolous patents, as these will be vulnerable to invalidation proceedings. Providing temporary exclusivity as an incentive to generic applicants under such a procedure may be detrimental, as applicants may reach agreements with innovators that result in a delay in marketing the generic. Alternative incentives could include temporary exclusive selling rights to state healthcare initiatives, effectively awarding generic applicants a considerable share of the market upon entry, although this could adversely affect prices in the short term.

Domestic generics firms that gain litigation experience by invalidating patents locally can use this experience to invalidate foreign patents and enter lucrative

markets in developed countries. Therefore, provisions along the lines of Paragraph IV will be beneficial to the development of generics firms as well as public health.

It must be noted that Patent Listing systems can also create barriers to entry by requiring generics firms to state their intentions regarding the respective originator's patents. Such provisions are not necessary for non-contentious ANDAs and will only discourage generic competition. Therefore, ANDA applicants should not be required to state their intentions unless they wish to contest the validity of a patent or seek a declaration of non-infringement.

### **7.9 Bolar Exceptions**

It is recommended that following the outcome of *EU v Canada* in the WTO that countries should introduce Bolar exceptions into their legislation, as it legitimately affords generics manufacturers the right to begin testing a patented product before patent expiry.<sup>82</sup> In addition, a Bolar provision would allow ANDA applications to be submitted before the expiry of patents and data exclusivity, which will allow authorities enough time to evaluate the ANDA, increasing the chances of approval immediately or shortly after the expiry of the relevant patents, allowing the generic to enter the market as soon as possible. Stockpiling, however, is not permitted, and therefore mass production of a generic will generally not begin until the relevant patents expire.

### **7.10 Patent Term Extensions**

Patent term extensions are common in developed countries, and offer a considerable economic advantage to innovatory firms. These extensions are designed to compensate firms for the time and expense lost during the regulatory process. As these are not necessary under TRIPS, it is not recommended that developing countries enact such provisions, as this will delay the entry of generic drugs onto the market. An advantage this offers to firms in developing countries is

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<sup>82</sup> BARTON, J *et al.* (2003). *Integrating Intellectual Property Rights and Development Policy*. (3rd Ed.). Commission on Intellectual Property Rights. Available from: [http://www.iprcommission.org/graphic/documents/final\\_report.htm](http://www.iprcommission.org/graphic/documents/final_report.htm)

that patent monopolies will end in the country concerned before they end in most developed countries with PTE provisions. This means that such generics firms can stockpile drugs for export to developed countries, which gives them a significant advantage on a global scale. This is one of the reasons that Indian firms have been successful in the global generics market, and continuing to take advantage of such provisions will allow generics industries in developing countries to expand into foreign markets, and eventually evolve and develop research capacity.

## **8. Concluding Remarks**

The above suggestions are a few possibilities among the many available to developing countries in the formation of their legislation. The wording of Article 39.3 allows countries considerable flexibility, which countries will have to take advantage of if they want to achieve their goals of improving public health and economic development.

The evolution of legislation in developed countries is a useful reference in predicting the effects of certain legislative measures. Analysing the relative strengths and weaknesses of legislative measures in the two major developed jurisdictions, Europe and the US, helps to determine the effects of varying certain provisions. In addition, the long established provisions in the competitive US market provide a good indication of the potential loopholes that can occur, and how firms will exploit them.

The prevention of the unethical exploitation of biological resources by corporations is an issue of increasing importance. If countries are to allow bioprospecting and the exploitation of biological resources, they must ensure that this is done equitably and without adversely affecting the local ecology. The ambit of data exclusivity measures can contribute to the incentives for firms to engage in such activities, and countries will have to take this into account when formulating policies regarding such matters.

Although many have criticised measures in developed countries as being too strong for developing countries to use, certain measures such as ANDA procedures and Bolar exceptions have proved beneficial to generics in the developed world, and developing countries should not ignore them. The benefits of such measures will significantly outweigh the limited provision of data exclusivity, which is required in order to ensure the compliance of any ANDA provisions with TRIPS.

Also patent listing, which is often seen as a TRIPS-plus measure, can easily be tailored to remove the associated entry barriers while still providing the benefits of increased transparency regarding originators' patents, together with the possibility

for contentious ANDA procedures which will encourage generics manufacturers to challenge patents.

Developing countries will have to use concepts from developed countries alongside their own measures, such as summary applications and compulsory licensing, to produce an economic environment that is beneficial to public health and generics manufacturers. Such manufacturers are important for producing generic drugs locally and fostering independence from foreign multinationals. In addition, promoting the interests of generics companies will allow the native pharmaceutical industry to grow, eventually penetrating the markets of developed countries and providing useful research channels that will be important for countries' future economic development.

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