

The Invention of an Investment Incentive for Pharmaceutical Innovation

Shamnad Basheer

West Bengal National University of Juridical Sciences

Pharmaceutical drugs are often hailed as the poster child for the proposition that patents foster accelerated rates of innovation. This sentiment stems, in large part, from the belief that pharmaceutical research and development (R&D) entails significant costs and resources. I argue that if the role of the patent regime is one of fostering higher amounts of investment in the R&D process, it is better served by a direct investment protection regime, where the protection does not depend upon whether or not the underlying idea behind the drug is “new” and “inventive”, two central tenets of patent law. Rather, any drug that successfully makes it past the regulatory filter ought to be entitled to protection, since its discovery and development entail significant investment and risk.

Owing to the sub-optimality of the current patent regime in protecting intensive pharmaceutical R&D investments from free riders, I propose a comprehensive investment protection regime that helps recoup all investments incurred during the drug discovery and development process. Though similar to existing data protection regimes in some respects, it differs in others. Firstly, it enables a recovery of all R&D costs, and not only costs associated with clinical trials. Secondly, unlike patents and data exclusivity, which offer uniform periods of protection, it rewards investments in a proportionate manner, wherein drug originators are entitled to protection against free riders only until such time as they recoup their specific investments and earn a rate of return on investment dependent *inter alia* on the health value of the drug.

I consider a pure market exclusivity based investment protection regime but note that it is likely to foster excessive pricing and subject the market to the dictates of a single firm. In the alternative, I consider a compensatory liability model based on a novel cost sharing methodology, where follow-on entrants are free to manufacture the drug, but must pay a reasonable amount of compensation to the originator. Lastly, I consider a reimbursement model, where the costs of drug discovery and development are reimbursed through public funding and prizes.

Once it is appreciated that the function of investment protection is better addressed through a separate regime, the pressure on patents to fulfil a role for which it is not intrinsically suited, abates. This point is an important one to appreciate, as the conflation between patent protection and investment protection has caused many to argue for a dilution of the patentability threshold.

Keywords innovation; patent; pharmaceutical; TRIPS

Most developed nations resort to two key legal instruments to incentivize pharmaceutical innovation, namely patents and data exclusivity. In this article, I investigate the optimality of these legal regimes to foster pharmaceutical innovation. Finding that they suffer serious shortcomings, I propose a novel investment protection regime.

As far back as 1976, a commentator noted that “[w]ithout patents, the return from investment in pharmaceutical research and development would fall to zero, and private companies would no longer engage in research and development” (Schwartzman, 1976).

This sentiment continues unabated till this day, and even those that question the general nexus between patents and innovation admit that the pharmaceutical industry is an exception (Roin, 2009; Landes and Posner, 2003, p. 316).¹ Illustratively, Bessen and Meurer, two of the most vocal critics of the patent system, note that “(i)n some industries, such as pharmaceuticals, patents provide strong

positive incentives to invest in innovation. But in many other industries, perhaps most, patents fail to perform like property and they may actually discourage innovation” (Bessen and Meurer, 2008a, p. 19; Bessen and Meurer, 2008b).

While this statement may hold true at a general level, I take issue with the underlying sentiment that patents serve as optimal investment inducing instruments. I argue that if the role of the patent system is conceptualized as one of fostering higher levels of investment into the pharmaceutical research and development (R&D) process, this function is more optimally achieved through a direct investment protection regime that does not depend on compliance with traditional patentability criteria such as “novelty” and “inventive step” (Barton, 2003).²

In other words, a regime that grants comprehensive market exclusivity to new drugs against free riders until such time as the investment in the discovery and development of that drug is recouped is preferable to a patent regime. I elaborate upon such a regime in the ensuing parts. This regime draws in some ways from existing regulatory data exclusivity regimes, which protect investment costs incurred in the course of generating regulatory data through clinical trials, that is, “safety” and “efficacy” data, which are required to be submitted to a drug regulatory authority to procure marketing approval (Mossinghoff, 1999). This regulatory data generation accounts for a major part of drug discovery and development costs (DiMasi *et al.*, 2003, p. 165). Countries such as the United States and the European Union countries (hereinafter “EU”) protect the investments underlying this data generation by granting a fixed term of market exclusivity, during which time no competitor can rely on the data submitted by the drug originator.

However, while a data exclusivity regime could be considered an explicit investment protection tool and is therefore more optimal than a patent regime on this count, it suffers from certain shortcomings. Firstly, it provides for a uniform period of protection, *sans* any consideration of the specific investment made per drug or the health impact of a drug. Secondly, it only accounts for the costs incurred during the clinical trial process and excludes significant investments made at the drug discovery and pre-clinical stages.

I advocate a comprehensive, yet calibrated investment protection regime that grants protection from free riders who threaten to disrupt the market share of the drug originator with a largely “similar” drug molecule, until such time as the investments are recouped along with a rate of return on the investment that broadly tallies with the cost of capital (CoC) and is commensurate with the health impact of the drug (hereafter referred to as an “appropriate rate of return”).

I first consider a standard market exclusivity model, and note its advantages and disadvantages. In the alternative, I consider a compensatory liability regime, which eschews any kind of market exclusivity, leaving the drug originator with the mere right to claim reasonable compensation from follow-on entrants.³ I propose a new framework for assessing fair compensation in this regard. I then consider a reimbursement model, where the costs of R&D are reimbursed through public funding and/or prizes.

Once it is appreciated that the function of investment protection is better addressed through a separate regime, the pressure on patents to fulfil a role for which it is not intrinsically suited, abates. This point is an important one to appreciate, as the conflation between patent protection and investment protection has caused many to argue for a dilution of the patentability threshold.⁴

Contribution

The key contribution of this article is in demonstrating that a comprehensive investment protection regime is far more optimal than the current patent and data exclusivity regimes in protecting the significant investments in drug discovery and development.

Although scholars have highlighted the limitations of the patent regime in supporting pharmaceutical innovation in an optimal manner, none have proposed a comprehensive investment protection regime, as that proposed in this article. Even those that focus on investment protection advocate the use of the data exclusivity regime. This article demonstrates the limitations of the data exclusivity regime, the most obvious of which is that the protection is tied to the submission of regulatory data and is meant to cover only those costs incurred during clinical trials. More importantly, data exclusivity regimes offer uniform periods of protection, which may either under-compensate or over-compensate the drug originator.

Lastly, the article considers a novel compensatory liability model in order to thwart potential abuses of the granted monopoly by drug originators who price drugs excessively and/or fail to supply the market adequately. Under such a model, drug originators do not have exclusive rights over their drugs; rather, follow-on innovators can enter the market and compete, upon the payment of reasonable compensation to the drug originator. The article proposes a novel methodology of computing compensation, whereby a reasonable amount, which balances the interests of both the drug originator and the follow-on manufacturer, is to be paid. The compensation methodology takes into account the global nature of pharmaceutical innovation and the international market for drugs.

Parts

The article proceeds as follows.

The section entitled “Drug Discovery and Development: An Overview” outlines the framework for pharmaceutical R&D in order to help appreciate the intensive nature of investments and risks underlying pharmaceutical innovation.

The section entitled “Patents, Innovation and Investment Protection” explores the role of patents in pharmaceutical innovation and points out why the regime is sub-optimal from the point of view of protecting investments.

The section entitled “Data Exclusivity and Pharmaceutical Innovation” discusses the data exclusivity regime (as prevalent in the United States and EU) and its nexus with pharmaceutical innovation.

The section entitled “Investment Protection Regime” outlines a comprehensive “investment protection” regime, under which drug originators are granted market exclusivity for a certain number of years after the drug has been approved. This period of protection is not a uniform one, but is based on the time taken by drug originators to recover the costs incurred in relation to each drug, as also an appropriate rate of return on investment based on the “health impact” of the drug, measured through existing metrics such as quality-adjusted life years (QALYs) and disability-adjusted life years (DALYs).⁵ Such a calibrated protection regime is more optimal from a policy perspective, as it avoids over-compensating or under-compensating drug originators. Most importantly, it helps prevent the proliferation of “me too” drugs⁶ through a process commonly referred to as evergreening.⁷

Owing to the potential dangers associated with market exclusivity, I also consider a compulsory licencing/compensatory liability regime, where the drug originator is not vested with exclusive rights over the relevant drug market. Rather, any follow-on generic competitor may enter the market upon the payment of equitable remuneration. I propose a novel compensatory methodology, taking into account the costs of drug discovery and development and the relative market shares of the originator and the follow-on generic entrant(s).

Lastly, I consider a reimbursement model as an alternative investment protection instrument, where the costs of R&D are reimbursed through public funding and/or prizes.

In the section entitled “Patents, Upstream Inventions and Incentives”, I note that despite the sub-optimality of the patent regime, member states cannot dispense with it, owing to the existence

of Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), an internationally binding legal instrument. However, countries are free to keep their patentability standard at fairly high thresholds. The last part concludes the article by highlighting the key arguments and proposals advanced.

Defining the Scope

For the purpose of this article, I define pharmaceutical innovation as the creation of any new drug or the discovery of any new indication or use for an existing drug, for which regulatory approval is required.

Secondly, the term “pharmaceutical drug”⁸ will be used to refer to conventional “small molecule” pharmaceutical drugs (hereinafter referred to as “conventional pharmaceutical drugs”) and to the newer wave of bio-pharmaceuticals (Rader, 2005, pp. 60–1)⁹ or biologics (Gitter, 2008, p. 560).¹⁰ However, given that the biologics sector is relatively nascent, the context in this article will be provided largely by specific examples from the conventional pharmaceutical industry.

Thirdly, this article deals primarily with incentives for fostering pharmaceutical innovation in developed countries such as the United States and the EU. The purpose behind this focus is twofold. Firstly, most originator drugs have their primary markets in these countries, and more often than not, drugs are attributable to firms headquartered in these countries. Secondly, most of the literature surrounding pharmaceutical innovation and incentives, particularly in relation to patents and data exclusivity relate to these jurisdictions. However, where relevant, other countries have been discussed in this article. Illustratively, it is noted that a compensatory liability model may be better suited for technologically proficient developing countries such as India.

A corollary of the above-mentioned focus on developed country markets is that the proposed investment protection regime is better suited towards fostering cures for diseases endemic to such countries, which I refer to for the sake of convenience as “developed country” diseases.

Lastly, this article aims to work within the current framework of the “TRIPS” and proposes models that are likely to be TRIPS compliant.

Drug Discovery and Development: An Overview

The drug discovery and development process is characterized by high risk and investment, as outlined in the sections “Stages of Drug Discovery and Development” and “Costs and Risks of Pharmaceutical Innovation”. I focus mainly on the US and EU regulatory frameworks.

Stages of Drug Discovery and Development

The process for bringing a drug to the market can be classified into three broad stages: (i) the discovery phase; (ii) the pre-clinical phase and (iii) the clinical trial phase (DiMasi *et al.*, 2003, pp. 151–5).

Discovery Phase

Since the “discovery” phase is what effectively heralds the concrete search for a new drug, it will be used in this article as the starting point of the timeline for the purpose of computing the costs associated with drug discovery and development. At its very core, this stage involves the search for a “target”, followed by that of a “lead” capable of acting on the target to cure the disease (Brodniewicz and Gryniewicz, 2010). A target is often a single molecule, such as a gene or a protein, responsible in large part for triggering the disease. Once identified, it has to be tested and its role in the disease confirmed and validated (Drews, 2000, pp. 1962–63).

After the target has been validated, the drug originator has to find a promising molecule (a “lead compound”) to act on the target in such a way as to inhibit the diseased condition. According to the

United States Food and Drug Association (hereinafter “FDA”) this is typically done by screening hundreds of thousands of chemical and biochemical substances that are likely to impact the target (FDA, 2011a).

Pre-clinical Phase

The pre-clinical phase involves testing an optimized lead in the laboratory (*in vitro*) (Macmillan Dictionary Thesaurus, 2011)¹¹ as well as on animals to determine its preliminary safety and efficacy. The data generated through the above experiments are then used to file an investigational new drug application (hereinafter “INDA”), an application requesting the FDA’s permission to test the drug on human beings (FDA, 2011b) The EU follows a similar procedure, where prior to conducting human trials, the sponsor must request a clinical trial authorization (hereinafter “CTA”; Foote and Wood, 2009).¹² After the relevant permission is granted, an IND/CTA applicant is entitled to initiate human trials, the most expensive stage in the drug development framework.

Clinical Trial Phase

The clinical trial phase entails three stages, each conducted on a progressively larger number of volunteers. Stage I of the clinical trials is carried out on a small number (between 20 and 80) of healthy human volunteers, primarily to determine toxicity and appropriate dosage (FDA, 2011c). Stage II of the clinical trials is carried out on a larger number (between 100 and 300) of “diseased” participants in order to gather data on the drug’s efficacy, along with further indications of side effects (FDA, 2011c). Finally, in Stage III, the drug is administered to a large number of volunteers (between 1,000 and 3,000), to firmly establish its efficacy, acquire more statistically significant results and determine the less common side effects (FDA, 2011c).

These steps are broadly similar to the EU regulatory process (Junod, 2004). The trials culminate in the filing of a new drug application (hereinafter “NDA”) before the drug regulator, which is then evaluated on several criteria, including the efficacy and safety of the drug in question, as also the severity of the disease in question (Bresnahan *et al.*, 2007).

Essentially, drug regulators such as the FDA follow a risk-benefit analysis, wherein a drug is considered fit for approval, if its benefits outweigh the risks (Bresnahan *et al.*, 2007). Often, drug applicants are subjected to a fourth phase as well, where they have to monitor the long-term use of the drug in specific patients, as well as the occurrence of rare side effects (Alzheimer Europe, 2009).

In short, the term “drug discovery” is used to refer to all stages involving the search for and identification of a disease target and the discovery of a lead to inhibit that target. “Drug development”, on the other hand, effectively begins with the pre-clinical phase (when the lead is subjected to laboratory and animal testing) and includes, as its major component, the clinical trial phase (phases 1–3).

Costs and Risks of Pharmaceutical Innovation

As can be inferred from the phases described above, the process of pharmaceutical innovation entails significant costs and a high risk of failure. It is estimated that less than 1% of the compounds examined in the pre-clinical phase make it to clinical trials (Fellmeth, 2004, pp. 443–95; Grabowski, 2002, p. 851). Of the compounds that make it to clinical trials, only 19% procure FDA approval (DiMasi *et al.*, 2010).

The number of failures during drug development has been constantly on the rise in the recent past. During the period 2001–6, the percentage of new products that were dropped after Stage II clinical trials (when drugs are first tested against a placebo) rose by 20%. During Stage III trials, that is, large-scale trials to test safety and efficacy, the failure rate increased by 11% (Silberman, 2009). It is also pertinent to note that despite significant investments in R&D, the FDA approved only 19 first-of-their-kind remedies in 2007—the fewest since 1983—and only 24 in 2008 (Silberman, 2009).

It is estimated that half of all drugs that fail in late-stage trials drop out of the pipeline due to their inability to beat placebos (Silberman, 2009).

Apart from the high risks, the drug innovation process entails significant costs as well. The most cited study in this regard (hereinafter “DiMasi study”) estimated that it would take approximately USD 802 million to produce a marketable drug (DiMasi *et al.*, 2003, p. 166). These estimates have increased, with the most recent figure amounting to approximately USD 1.3 billion (DiMasi and Grabowski, 2007; PhRMA, 2010; Tufts Centre for Study of Drug Development, 2001).¹³ However, given that drug companies have been reluctant to disclose their costs of drug discovery and development to the public, these costs remain a highly contested issue.

In 2001, Public Citizen, a civil society group in the United States, contested the above figures on several grounds, the most pertinent of which are highlighted as follows:

- (1) R&D costs should be regarded as an expense and not an investment. Therefore, the costs of capital are irrelevant (Public Citizen, 2001, p. 3).
- (2) The estimated cost did not take into account the decrease in FDA review time, lower clinical trial periods and the contribution of new technologies such as genomics and combinatorial chemistry, which are believed to have assisted in the lowering of costs involved in creating drug leads (Public Citizen, 2001, p. 4).
- (3) If one were to assume the veracity of the pharmaceutical industry’s self-reported total R&D figures between 1994 and 2000 and divide this amount by the total number of approved drugs (after controlling for time lag), one would arrive at a figure of USD 108 million per new drug before tax benefits and USD 71 million after, which is significantly lower than the DiMasi estimates (Light, 2007, p. 897).¹⁴

Donald Light additionally critiques the study on the ground that the numbers are based on a small sample of large pharmaceutical firms (Light, 2007, pp. 897–900)¹⁵ which were non-randomly selected, and include only new molecular entities (hereinafter “NME”), the most costly sub-group of pharmaceuticals that constitute only one-third of new drug approvals (Light, 2007).¹⁶ He argues that if the costs of other “incremental” drugs (constituting three-fourths of all drugs) were taken into account, the average cost of a drug would fall to USD 400 million (Light, 2007, p. 896).¹⁷

Notwithstanding the veracity of DiMasi’s figures, there is no gainsaying the fact that the conduct of clinical trials and the generation of data relating to safety and efficacy is an expensive process, when compared with the costs of market entry for other technology products such as electronics and software. The question of appropriately protecting these investments from free riders is, therefore, an urgent one meriting serious consideration.¹⁸

Patents, Innovation and Investment Protection

The debates on innovation policy are inextricably woven with references to the patent regime, often seen as the primary legal incentive for technological innovation (Burk and Lemley, 2003, p. 1575).¹⁹ At its very core, the patent system seeks to foster new and non-obvious inventions by granting a limited legal monopoly (Hall, 2007, p. 568; Parchomovsky and Wagner, 2005, pp. 13–4).²⁰ The theories underlying the patent system are many, and I focus on the most important one below (Fisher, 2001, pp. 168–200).

Incentive Theory

The most prevalent justification for the patent system is offered by the “incentive” theory that stipulates that patent rewards (in the form of 20-year monopolies) incentivize prospective inventors

to accelerate their inventive efforts, than would be the case without patents (Fisher, 2001, pp. 168–200).²¹ In other words, patents are likely to increase the rate of generation of new and useful ideas for society. Although some may argue that new ideas and inventions are likely to be generated even without patents (Boldrin and Levine, 2005),²² the key question to be answered is: would the rate of generation of such new ideas be the same in the absence of a patent system?

The prevalence of the incentive theory notwithstanding, it is yet to find strong empirical support (Mansfield, 1986, pp. 173–81; Tomlinson and Torrance, 2009, p. 132).²³ Bronwyn H. Hall concludes that although a stronger patent system is likely to result in an increase in patenting, it is not clear if these changes will also simultaneously result in an increase in innovative activity (Hall, 2007, p. 574).

While assessing the role of patents, one must also consider the “social” costs of patents i.e. the fact that patents are capable of decelerating or slowing down innovative progress by “blocking” competition, particularly downstream research and improvements (Lemley, 2001, p. 1515).²⁴ This potential for blocking has been documented through specific historical examples in a seminal piece by Merges and Nelson (1990, pp. 885–87, 890–91) and in a later equally seminal piece by Heller and Eisenberg (1998, pp. 698–701). Merges and Nelson refer to broad patents covering technologies underlying Edison’s light bulb, the Wright Brothers’ airplane and Selden’s automobile engine to buttress their claim that overbroad patents effectively retarded technological progress.²⁵

While assessing the role of the patent system in fostering innovation, scholars often point to the fact that significant investments and efforts may be required to translate certain inventive ideas into commercially useful products (Duffy, 2004, p. 440; Kitch, 1977; Scherer, 1980, pp. 440–1).²⁶ Indeed, an inventive idea has little use to the public, unless it has been developed into a marketable product (Sichelman, 2010, p. 343).²⁷ While this developmental cost may be modest in some cases,²⁸ it is significant in others. But this by itself does not necessarily make out a case for patent protection. Firstly, it is possible that the technological product that is finally developed enjoys a significant lead-time over competitors and consequently a *de facto* market monopoly till such time as a rival enters the market (Mazzoleni and Nelson, 1998, p. 1048).²⁹ Secondly, it might be the case that a competitor is compelled to spend an amount equivalent to that of the original innovator in developing the product and is, therefore, dissuaded from entering the market (Scherer, 2007, pp. 27–8).³⁰

In other cases however, it is possible that the investments are significant, the lead-time advantages insufficient and the costs of making copies significantly lower than that of the originator product. Pharmaceutical drugs are illustrative of this, where firms may be reluctant to invest in R&D, in the absence of some form of legally sanctioned market protection.³¹

For this reason, scholars such as Hall carve out an exception for the pharmaceutical industry, noting that that in such industries, patents are likely to foster investments and, thereby, the rate of innovative output as well (Hall, 2007, p. 568). I argue that if our expectation from the patent regime is that it would induce a higher rate of investment and consequently a higher rate of innovation, then that function is more optimally achieved through a direct investment protection regime. In other words, rather than relying on a sub-optimal patent regime, I advocate the institution of a comprehensive investment protection regime.

Pharmaceutical Patents and Innovation

The above discussion notes that the “incentive” theory, often the most widely cited and relied upon, fails to drum up persuasive empirical evidence in its support. However, scepticism about the nexus between patents and innovation notwithstanding, most ardent critics readily admit that the pharmaceutical industry is an exception (Kingston, 1987, pp. 30–2).³² Illustratively, Bessen and Meurer, two of the most vocal critics of the patent system note that “In some industries, such as pharmaceuticals, patents provide strong positive incentives to invest in innovation. But in many

other industries, perhaps most, patents fail to perform like property and they may actually discourage innovation” (Bessen and Meurer, 2008a, p. 19).

Courts have also endorsed similar sentiments while adjudicating upon the validity of pharmaceutical patents. In *Sanofi-Synthelabo v Apotex Inc.*,³³ it was observed that “[w]e have long acknowledged the importance of the patent system in encouraging innovation . . . Importantly, the patent system provides incentive to the innovative drug companies to continue costly development efforts”. Implicit in the above statements are two assumptions:

- (1) That a higher rate of investment in R&D will trigger more innovative output and
- (2) that the patent system is optimally suited towards incentivizing higher rates of R&D investment.

It is difficult to quibble with the first sentiment, as it is logical to assume that, *ceteris paribus*, in an industry characterized by expensive R&D such as pharmaceuticals, a higher rate of investment is likely to accelerate innovative output (Merges and Nelson, 1990, pp. 871, 916).³⁴ However, the second assumption calls for critical interrogation. For, if investment protection is the goal, it ought not to depend upon whether or not the underlying idea behind the drug is “new” and “inventive”,³⁵ the two central tenets of patent law.³⁶ Rather, any drug that makes it past the regulatory filter ought to be entitled to such protection, since the discovery and development of all approved drugs entail significant investment (Reichman, 2009, p. 43).³⁷

The Sub-Optimality of Patents

Patent regimes, which aim to protect new and non-obvious inventions, are not intrinsically suited towards the protection of investments underlying innovative products. The various deficiencies in this regard are outlined as follows.

The Patentability Threshold

That patents, in their current avatar, do not always translate to optimal investment protection instruments is evident when one considers the simple fact that several patented ideas and, products based on them may have emerged with meagre investment.³⁸ As a corollary, an idea, though widely known, may still require significant investment before being converted into a useful product. Illustratively, a molecule that is either known (through publication in scientific journals) or obvious in the light of prior art and therefore, un-patentable may still entail extensive development costs (associated with clinical trials and the like) prior to being converted to a marketable drug (Roin, 2009, pp. 553–4).³⁹

Consider Pfizer’s patent covering Sildenafil Citrate, a known PDE V (phosphodiesterase isoenzymes, Type V) inhibitor (Stief, 2000)⁴⁰ that turned out to be a path-breaking treatment for male erectile dysfunction (MED) and was voted as one of the brightest British innovations of the 1990s.⁴¹ Viagra, Pfizer’s brand name for the active ingredient, Sildenafil Citrate, was the first effective oral treatment for MED, now prescribed in more than 90 countries worldwide and is by far the most widely used treatment for the condition, with up to 82% of patients experiencing benefits (Flower, 2002, p. 17).

At the time of this path-breaking discovery, Sildenafil Citrate was already a known substance and was being tested by Pfizer for its ability to cure angina (blood pressure) and a specific form of heart ailment. Upon discovering its potential new use as a cure for MED, Pfizer immediately filed a patent.⁴² The UK courts, however, invalidated the patent on the ground that the new use would have been obvious to a person skilled in the art.⁴³ The court based its reasoning on the ground that the prior art included certain published patents⁴⁴ as also an article by Rajfer *et al.* that, when combined, taught that Sildenafil Citrate, a known PDE VA inhibitor could be useful for the treatment of MED.⁴⁵

Although the claimed invention was held obvious under English patent law, it is important to appreciate that the development of Sildenafil Citrate into a marketable drug would have necessarily

entailed the infusion of significant investment in terms of time, effort and money. Unfortunately, current patent standards do not protect such raw investments. As a commentator rightly notes:

The novelty and non-obviousness requirements make no concession for the development costs of inventions and thus cause patents to be withheld from drugs that are unlikely to reach the public without that protection. This gap in the patent system for drugs has created a pervasive problem in the pharmaceutical industry, causing firms to regularly screen their drugs during the research-and-development process and discard ones with weak patent protection (Roin, 2007, pp. 28–9).

To this extent, an investment protection regime that directly protects the investment by *inter alia* preventing competitors from entering the market till such time as the investments are recovered would appear to be more optimal than a patent regime.

The Uniformity of a Patent Regime

Most patent regimes offer a standard 20-year term of protection to all inventions, without any regard to inventive merit, social value or the large investments underlying the invention. This uniform period of protection is mandated by article 33 of TRIPS.⁴⁶

Some countries have adapted these uniform patent term periods to suit the peculiarities of pharmaceutical innovation, where there is a considerable time lag between the grant of a patent to a pharmaceutical invention and its final development into a drug that is approved for marketing. Countries have therefore amended patent regimes to make good the loss of term protection occasioned by such intensive regulatory processes. Popularly known as “patent term extensions”, these additional periods of protection are added on to the regular patent protection (Schacht and Thomas, 2002, p. 2).

However, patent term extensions effectively endorse the uniform 20-year protection period and merely attempt to make up for the time lost out during the regulatory process. An investment protection regime that compensates for a time period equivalent to the time that it actually takes to recoup all investments pertaining to drug discovery and development is far more optimal than a uniform period of legal protection.

The Relative Indeterminacy of Patent Standards

I argue that the patentability threshold, most notably the non-obviousness criterion, is relatively indeterminate (Mullally, 2010, pp. 1135–42; Petherbridge, 2010, p. 907)⁴⁷ and ill-suited for protecting investments (Lane, 1987, p. 1159).⁴⁸ Apart from this, issues such as claim scope and the applicability or otherwise of the doctrine of equivalents add to the general indeterminacy and uncertainty surrounding the patent regime (Brill, 2008).⁴⁹ It is not my intention to explore all areas of indeterminacy in patent law but merely to focus on one of them, namely, the non-obviousness or inventive step criterion with a view to demonstrating that the patent regime is relatively more indeterminate than a comprehensive investment protection regime (which protects all drugs that have received regulatory approval, without requiring further thresholds to be met).

At its core, the non-obviousness threshold in patent law seeks to exclude all alleged inventions that would have been “obvious” to a person skilled in the art imputed with knowledge of all prior art up to that stage. This determination is easier said than done, for the distance between the prior art and the claimed invention is a matter of degree and prone to some amount of subjective assessment.⁵⁰ This is particularly so in the context of pharmaceutical and biotechnology inventions, where the element of uncertainty is higher than other technological domains (Minssen, 2010). A wide array of cases in the United States and other key jurisdictions bear this out. Illustratively, consider the *Escitalopram* case involving a patented pharmaceutical enantiomer (Darrow, 2007).⁵¹ While the United Kingdom,⁵²

German,⁵³ Canadian⁵⁴ and Australian courts⁵⁵ adjudicated the patent to be a valid one, the Dutch court held that the patent was invalid for obviousness.⁵⁶

Another instance of divergent interpretation of the obviousness criterion is illustrated by the *Viagra* case, discussed earlier in this Part.⁵⁷ The UK courts invalidated the patent on the ground that it was obvious in the light of prior art, which suggested the utility of the claimed PDE VA inhibitor in potentially curing erectile dysfunction. However, the Federal Court of Appeal in Canada rejected the above line of reasoning and held that a mere “worth a try” possibility did not preclude inventiveness. Rather, the claimed invention would be obvious, only when the “try” was a matter of routine and required no significant thinking or effort.⁵⁸

The divergent conclusions on obviousness discussed above stem not only from a differential subjective assessment of the same facts,⁵⁹ but also from a difference in legal standards. As can be seen from the above discussion, Canada preferred a lower inventive step threshold than the United Kingdom.⁶⁰ In fact, there is a common perception that courts in the United Kingdom are relatively less friendly to patent owners than their European counterparts such as Germany.⁶¹

While such divergent interpretations and consequent uncertainty are not exclusive to patents but common to other areas of law, the degree of variance is likely to differ, with patents tending towards greater indeterminacy. Critical legal scholars point to this indeterminacy in decision making (Kairys, 1984, pp. 244, 247; Kennedy, 1976, p. 1700), noting that judges are free to choose from a variety of rules that apply to a particular case, rendering the decision making process rather uncertain (Kairys, 1984; Kennedy, 1976; Tushnet, 1983).

Others however take issue with a strong indeterminacy thesis, arguing that there are several “easy” cases in which legal rules have determinate applications (Solum, 1987, p. 471). While this may be so, it is evident that most patent disputes involving complex issues of non-obviousness do not sit comfortably within the “easy” category and will tend towards greater indeterminacy.

Contrast this with a direct investment protection regime, which is likely to be more determinate in its application. However, I do not claim to measure this difference in “determinacy” between a patent regime and an investment protection regime with empirical precision. Rather, the suggestion is that the obviousness test is likely to entail a relatively greater amount of indeterminacy when compared with a direct investment protection regime as that proposed in this article, both in terms of the legal standard,⁶² as also in terms of its application to the facts.⁶³

A scholar argues that this indeterminacy in patent standards leads to inefficiently low incentives to research and develop great advances, and excessively high incentives to invest in mundane innovation (Mandel, 2008, p. 60). In much the same vein, another scholar argues that the indeterminacy “contributes significantly both to the insecure commercial value of many patents and to the cost of litigating their validity” (Cornish, 1983, p. 771).⁶⁴

For all of the above reasons, an explicit investment protection regime that grants legal protection commensurate with the level of investment, such that the investor is able to ward off free riders until such time as she recovers the investment and makes an appropriate rate of return depending on the health value of the product is better than the current patent regime.

Put another way, if high risk and large investments are the key reasons for desiring legal protection from free riders, it is more optimal to protect such investments directly, rather than shoehorning them into the inventive step criterion, which has been largely framed as a “cognitive” enquiry (Abramowicz and Duffy, 2011, p. 1592).⁶⁵

The Risk of Diluting Patentability Criteria

As mentioned earlier, any attempt to shoehorn an investment-based rationale into the existing patent framework is likely to lead to a lowering of the patentability threshold. Illustratively, Merges advocates

a “moderate lowering of patentability standards for very high cost research” (Merges, 1992).⁶⁶ Similarly, another reputed law and economics scholar, Suzanne Scotchmer suggests that “it is not inconceivable that patent offices could consider costs in their interpretation of non-obviousness” while granting patents (Scotchmer, 2004, p. 10).

Most tellingly, a judge of the Court of Appeals for the Federal Circuit in the United States in *Pfizer Inc. v Apotex* notes:

Many if not most pharmaceutical inventions are discovered through a routine screening protocol or through an established trial and error process. Pharmaceutical inventions discovered by these routine-screening methods include not only new formulations and salt forms, but also include the active pharmaceutical compounds themselves. Thus, this decision calls into question countless pharmaceutical patents, which in turn could have a profoundly negative effect on investments into the design and development of new life-saving pharmaceuticals.⁶⁷

I question this misconceived sentiment.⁶⁸ If investment protection is the goal, current patent law and doctrine are ill-suited for achieving it. Lowering the novelty and inventive step threshold would dilute the very essence of the patent regime, namely the protection of new and inventive ideas.⁶⁹

This brings to mind the classic Aristotelian distinction between essence/kind on the one hand, and attributes/quality on the other (Vaver, 2003). The inventive step filter lies at the heart of patent philosophy and it may in many ways, constitute its essence (Rich, 2004, pp. 181–192).⁷⁰ If this were to wither away, it would be disingenuous to pretend that one continues to work within the bounds of a patent regime.

The investment protection regime advocated by this article bears some resemblance to existing “data protection” regimes,⁷¹ which protect investments underlying the generation of regulatory data, that is, “safety” and “efficacy” data that are required to be submitted to a drug regulatory authority to procure marketing approval.⁷² This data generation from the various clinical trials accounts for a major part of drug discovery and development costs (DiMasi *et al.*, 2003, p. 165). The next part discusses and critically assesses the data exclusivity regime and its suitability as a comprehensive investment protection instrument.

Overview of Discussion

Based on the limited empirical evidence generated till date, it would appear that patents play a very limited role in fostering innovation. Any prospect of incentivizing innovation ought to be weighed against the “costs” of operating the patent regime (costs to patent applicants, competitors and the government) and the “social” costs of the system in general, whereby patents potentially stymie the downstream development of technology,⁷³ reduce levels of competition and cause deadweight losses (Banik and Kesan, 2000, p. 24).⁷⁴ Seen in this light, the case for a patent system is rather weak.

Scholars however treat the pharmaceutical industry as an exception, noting that the high costs endemic to the industry warrants the institution of a patent regime that prevents free riding. I critique this line of thinking, arguing that if the purpose is to simply enhance levels of investments in pharmaceutical R&D, this is better served by a direct investment regime that protects investments from free riders. Patents are not optimally suited for this purpose, suffering as they do from a number of drawbacks. Firstly, they protect only certain kind of inventions that are “novel” and “inventive”, without regard to the fact that a number of inventions that fail these patentability thresholds may still entail significant developmental costs. Secondly, the patent regime is relatively less determinate than an investment protection regime.

Thirdly, the costs of administering the patent system are likely to be higher than a more determinate investment protection regime. Fourthly, patents are granted to all new inventions for a uniform term without regard to the “value” of the invention and the amount of costs incurred in discovering the invention or developing it. Lastly, any attempt to adapt the patent regime and convert it to a comprehensive investment protection regime destroys its core essence i.e. protecting new and non-obvious inventions.

In short, it is far more optimal to institute a comprehensive investment protection regime for fostering higher levels of investment into pharmaceutical R&D. One might argue that a determination of the kinds of investment that are to merit protection and the baseline for such protection will prove difficult. While this may hold true within a general innovation context, it is more amenable to an objective determination within the pharmaceutical technology sector, where drugs are subject to a rigorous regulatory framework and cannot be marketed until approved (Eisenberg, 2007).

Data Exclusivity and Pharmaceutical Innovation

A number of countries protect the significant investments underlying clinical trial data by stipulating that data submitted by a drug originator to gain marketing approval cannot be relied upon by the drug regulator to approve any other drug for a certain period of time (IFPMA, 2005).⁷⁵ This effectively creates a period of market exclusivity for drug originators and is commonly referred to as “data exclusivity”. The next sections discuss the current data exclusivity regimes in the United States and EU.

Overview of Data Exclusivity Regime

Regulatory norms the world over stipulate that no new drug can be introduced in the market without the approval of the drug regulator. Illustratively, in the United States, firms are required to file an “NDA” before the drug regulator (FDA)⁷⁶ and submit extensive clinical trial and other data to demonstrate the safety and efficacy of their drug.⁷⁷ However, the process for approving a generic is far less complex, with an applicant having to simply file an abbreviated new drug application (hereinafter “ANDA”) demonstrating their generic version to be bio-equivalent to the existing originator drug.⁷⁸

Proof of bio-equivalence obviates the need to undertake fresh clinical trials by the generic applicant. Consequently, a generic manufacturer can introduce a follow-on drug into the market by expending far less resources than the drug originator.

In order to prevent such free riding, a number of legal regimes stipulate that the data submitted by an originator cannot be relied upon to approve a generic version for a certain minimum number of years. The extent and length of protection varies between the different countries and depends, in part, on the kind of drug/indication sought to be approved.

Overview of Data Exclusivity Regimes in the United States and EU

As a general rule, most new pharmaceutical drugs are granted 5 years of data exclusivity in the United States.⁷⁹ Apart from this, certain categories of drugs or indications merit additional periods of exclusivity such as orphan drug exclusivity,⁸⁰ pediatric exclusivity⁸¹ and exclusivities for new indications.⁸²

The EU provides a uniform period of protection for most new drugs. Commonly referred to as the 8 + 2 + 1 rule, it works as follows:

- (1) Abridged applications (by follow-on competitors) can be filed only after 8 years have elapsed from the approval of the reference product. However, abridged applications cannot be approved till at least 10 years have elapsed from the approval of the reference product.⁸³

- (2) The above period is extendable by another year if the original marketing authorization holder obtains authorization for a new therapeutic indication with significant clinical benefit.⁸⁴

Biologics and Data Exclusivity

The above rules pertain to conventional pharmaceutical drugs (Rader, 2005), where the equivalence between the chemical composition of an originator drug and its generic version is relatively easy to determine. However, in so far as biologics or bio-pharmaceuticals (Rader, 2005) are concerned, there continues to be considerable uncertainty about whether or not a mere demonstration of bio-equivalence would suffice to demonstrate “sameness” in efficacy and toxicity. For, biologics are larger in size and more complex in structure than conventional chemical molecules (Johnson, 2010) and a small change in process of manufacture could change the properties to a significant extent (Morgan, 2010, p. 96; Tzeng, 2010). The Hatch-Waxman Act, which provides for an abbreviated regulatory pathway for generics based on a demonstration of bio-equivalence, applies only to conventional small molecule drugs and not to biologics (Tzeng, 2010).

After much debate and considerable lobbying in the US, the Public Health Services Act, which deals with biologics, was amended to provide an abbreviated regulatory pathway for follow-on biologics that were ‘highly similar’ to the reference product.⁸⁵ Under this new regime, a follow-on entrant has to demonstrate close similarity to an approved biologic product and establish purity, safety and efficacy through clinical or laboratory based studies.⁸⁶

The new law also provides that the reference product is entitled to 12 years of data exclusivity, a substantially longer period than the 5 years available for conventional pharmaceutical drugs under the Hatch-Waxman Act.⁸⁷

As for the EU, it appears to have resolved this issue prior to the United States by providing in its 2004 directive for abridged authorizations of biological medicinal products that were ‘similar’ to the reference product.⁸⁸ However, the length of data exclusivity is the same as that provided for small molecule conventional drugs.

Notwithstanding the relative ease of operation of data exclusivity regimes when compared with a more indeterminate and expensive patent regime, the current framework suffers from significant infirmities, as discussed below.

Data Exclusivity and Innovation

Emerging as they do out of a regulatory framework aimed at producing safe and effective drugs, data exclusivity norms share a unique position in the pharmaceutical innovation matrix. Essentially, they seek to compensate a drug originator for the significant costs associated with the generation of clinical trial data. Legal incentives for data generation, therefore, not only promote consumer welfare by aiding the regulatory process, but also play a significant role in pharmaceutical innovation by fostering the production of new innovative drugs (Eisenberg, 2007, pp. 372–3, 388).

It is logical to assume that the level of investment made by a drug originator will depend to some extent on the scope of protection granted against free riders (Merges and Nelson, 1990, pp. 871, 878). Some scholars suggest that this common sense wisdom has been endorsed by the success of the ODA (Merril, 1996, p. 1791).⁸⁹

When compared with the patent regime, the data exclusivity regime appears better suited for protecting investments in pharmaceutical R&D. For one, a data exclusivity regime is relatively more determinate than existing patent regimes. Upon successful FDA or other regulatory approval, the drug in question is automatically entitled to an exclusivity period. The only issue for determination is the type of exclusivity that the drug is entitled to.

In contrast, a patent can be granted only when it is established that the claimed substance is patent eligible and patentable (Pila, 2003).⁹⁰ These pre-requisites have been the subject matter of

countless legal disputes, resulting in a grant process that is often uncertain, expensive and time consuming.⁹¹ While the drug regulatory process (and data exclusivity norms in particular) is also susceptible to interpretative disputes, it is relatively more determinate and less expensive to administer than the patent system. Secondly, and perhaps, more importantly, while a patent system rewards the mere prospect of an innovation (Sichelman, 2010, p. 342),⁹² a data exclusivity regime rewards only instances of successful innovation, that is, the final drug approval (Heled, 2012, pp. 468–9).⁹³ Further, while data exclusivity norms only prevent a direct competitor from entering the market with a same or similar drug, patents could potentially block downstream drug development (Eisenberg, 2007, pp. 365–6).

Owing to these various differences, scholars favour data exclusivity over patents (Eisenberg, 2007, p. 364).⁹⁴ However, notwithstanding the relative advantage of data exclusivity regimes over patent systems, such regimes also suffer serious drawbacks, as discussed in Section “Problems with Prevalent Data Exclusivity Regimes”.

Problems with Prevalent Data Exclusivity Regimes

Firstly, data exclusivity regimes are sub-optimal in that they set a “uniform” level of protection for all drugs, for the most part. For example, the United States provides new “conventional” pharmaceutical drugs with 5 years of data exclusivity, while the EU provides a uniform 10 years for most conventional drugs. There is no persuasive evidence to suggest that any of the above time frames appropriately protect the significant investments made in drug development (National Academics Committee on Science, Engineering and Public Policy, 2007, p. 190).⁹⁵ More importantly, the assumption that a uniform period of protection across all categories of drugs would appropriately protect investments for each drug is flawed.⁹⁶ A far more sensible policy is to compensate the originator to the extent of actual expenses incurred in relation to a particular drug.

Secondly, existing data exclusivity regimes are deficient in that they aim to compensate only those investments incurred during the clinical trial process, and not the significant expenses undertaken during the upstream levels of drug discovery. As noted earlier, of the total USD 802 million stated to be the average cost associated with drug discovery and development, the costs associated with the drug discovery phase amount to USD 335 million, which is not an insignificant amount.⁹⁷

I therefore argue that a comprehensive investment protection regime, as recommended in this article is a far more optimal instrument than the current data exclusivity framework.

Investment Protection Regime

The central argument of my article is that when compared with patents and data exclusivity, a comprehensive investment protection regime is a more optimal instrument to spur investment in drug discovery and development.

I consider three alternative models of investment protection in this article:

- (1) A standard market exclusivity model, where the drug originator is granted a term of exclusivity during which no competitor can enter the market. The term of exclusivity is granted till such time as the drug originator recovers its total costs along with an appropriate rate of return on investment, dependant on the health value of the drug.
- (2) A compulsory licencing or compensatory liability model, where competitors can enter the market after paying a reasonable compensation to the originator.
- (3) A reimbursement model where the total costs of drug discovery and development (and an appropriate rate of return) are reimbursed through instruments such as public funding or prizes.

For any of these alternatives to work, the drug originator must be obligated to submit all costs relating to drug discovery and development. However, there are significant challenges in accurately estimating these costs, as outlined in the sections “Computing the Costs of Drug Discovery and Development” and “Submission of Information Relating to Profits”.

Computing the Costs of Drug Discovery and Development

Despite pharmaceutical patents being one of the most debated issues today (Jayadev and Stiglitz, 2010), the costs of drug discovery and development remain highly contested.⁹⁸ Apart from the fact that the USD 802 million figure (updated more recently to USD 1.3 billion) has been severely criticized for methodological flaws, it wrongly assumes that all drugs broadly entail similar levels of expenditure and effort.

The investment protection regime advocated in this article calls for costs per drug, that is, it requires drug originators to submit the total costs associated with the discovery and development of a particular drug. This is a more meaningful endeavour than attempting to identify an average ballpark figure covering an entire spectrum of drugs, as DiMasi and other scholars set out to do. Such costs would ordinarily include

- (1) all “discovery” and “development” expenses incurred in relation to a drug that is approved by a drug regulator;
- (2) all fixed costs for establishing the relevant manufacturing facility, provided the facility has been created specifically for the drug in question and
- (3) the costs of all tried and tested targets and leads in relation to a particular disease.⁹⁹

The terms “discovery” and “development” as used in the first category have already been defined in Part I of the article. While most commentators focus on the downstream drug development phase (the clinical trial phase), (Banacossa and Kermani, 2003; Sichelman, 2010, p. 387) it bears noting that the upstream drug discovery phase also entails significant expenditure. DiMasi *et al.* estimate that when compared to the total costs associated with drug discovery and development (USD 802 million), the costs of drug discovery (USD 335 million) are not significantly lower than that of drug development (USD 467 million; DiMasi *et al.*, 2003, p. 166).

The article, therefore, proposes an inclusion of all costs connected with both drug “discovery” and “development”. Part I defined “drug discovery” as the stage commencing with the search for a disease target. It is proposed that this be construed as the start of the discovery process and all costs from hereon be counted towards compensation through an investment protection model. This is a more realistic starting point for the discovery process than pre-clinical testing or an IND filing, stages that may make for a relatively easier cut-off, but ignore important steps which precede them.

In order to contextualize the discussion, consider the evolution of Glivec (Novartis Pharmaceuticals Corporation, 2012),¹⁰⁰ a path-breaking anti-cancer drug that is now the subject of a highly contentious patent litigation in India (Basheer and Reddy, 2008, pp. 235–38). Touted as a “wonder drug” (Buchdunger and Zimmerman, 2012), Glivec treats chronic myeloid leukaemia (hereinafter “CML”), a cancer of myeloid blood cells characterized by a proliferation of granulocytes in the blood and bone marrow. More than 90% of people with CML have an acquired chromosomal abnormality, called the Philadelphia Chromosome, caused by reciprocal translocations between chromosomes 9 and 22. These translocations result in a BCR-ABL fusion gene that codes an active tyrosine kinase protein, which in turn leads to uncontrolled cell proliferation.

A newly discovered molecule, Imatinib, was found to inhibit Tyrosine Kinase and thereby slow the progress of CML. However, given that Imatinib itself could not be optimized into a drug, Novartis was forced to find a variant that would work: to this end, it investigated and discovered the beta

crystalline version of a certain salt of Imatinib (Imatinib Mesylate) which went on become the active ingredient underlying the drug, Glivec.

The various steps in the discovery and development of Glivec could be broadly encapsulated as follows.

- (1) Discovery of the Philadelphia Chromosome (a genetic mutation found in patients with CML): 1960.
- (2) Discovery that the genetic abnormality results in a cancer-inducing kinase enzyme: 1980s (note that this enzyme is effectively the “target” that any potential drug must inhibit).
- (3) More than 400 compounds are screened to assess their potential for inhibiting the “target” enzyme: late 1980s.
- (4) Scientists identify STI471 (Imatinib) as the most promising “lead” for inhibiting the enzyme: 1992.
- (5) Novartis files a patent covering Imatinib (free base) and all pharmaceutically acceptable salts: 1993.¹⁰¹
- (6) Novartis files a patent covering the beta crystalline version of Imatinib Mesylate, the active ingredient underlying the drug, Glivec: 1997.¹⁰²
- (7) Glivec is granted FDA approval: 2001 (Novartis Pharmaceuticals Corporation, 2012).

Under the model proposed in this article, all costs beginning with Step (1) (discovery of the Philadelphia Chromosome) are to be included in the total costs of drug discovery and development, and therefore eligible for compensation (Basheer and Reddy, 2008).

Cost of Failure

Given that the proposed regime covers all drug discovery costs, it effectively compensates for failure as well. Failure in such a context refers to those leads that are tested for a particular disease, but do not make it past the regulatory filter. Typically, for every lead that makes it past the regulatory filter, there are several others that were also tested, but failed to demonstrate sufficient safety and efficacy as to merit regulatory drug approval. Given that such failures are routine in the drug discovery and development process, this article advocates for the inclusion of costs associated with such failures as well (Li *et al.*, 2008).¹⁰³

It bears reiteration that regulatory clearance is becoming increasingly difficult, with only about 19% of the drugs entering the clinical stage being finally approved by the US FDA (DiMasi *et al.*, 2010). The Pharmaceutical Research and Manufacturers of America (PhRMA) and the European Federation of Pharmaceutical Industries and Associations (EFPIA) exemplify the high rate of failure by noting that, for every 5,000 drugs tested, only five make it to clinical trials on an average, and of those five, only one is ultimately approved for patient use (Fellmeth, 2004, p. 495; Fox, 2010). Given this high regulatory risk, it is only fair that the cost of failed “leads” and targets be included, as this is a “legitimate” cost incurred even by the best of innovators (Abbott and Vernon, 2005, pp. 12–3). However, all costs have to necessarily relate to research pertaining to a specific “disease” and the search for an effective lead.¹⁰⁴

Excluded Costs

The above discussion focussed on the kind of costs that ought to be recompensed under an investment protection regime. It is equally important to discuss costs that ought to be excluded in order to avoid over-compensating the investor. Firstly, costs that have already been claimed in relation to an originator drug cannot be reclaimed for a second derivative drug.¹⁰⁵ By way of example, any R&D expenses incurred in relation to the development of Prilosec ought to be excluded from the costs associated with its derivative, Nexium. Both are proton pump inhibitors developed by Astra

Zeneca to cure acidity.¹⁰⁶ Secondly, as discussed earlier, any public funds made available to the drug originator ought to be deducted from the overall costs of drug discovery and development, while assessing the extent of protection owed to such drugs under the proposed regime.

Thirdly, given the fact that drug companies have often been accused of spending excessive sums of money on marketing their drugs including *inter alia* by lavishing gifts on doctors who are then persuaded to prescribe their expensive originator versions (Angell, 2004, p. 120; Weiss, 2010),¹⁰⁷ the investment protection model ought not to protect such costs. The industry claims that these are legitimate costs incurred to educate doctors and consumers (PhRMA, 2008).¹⁰⁸ However, as scholars note, any perceived advantages from such alleged information campaigns are vastly outweighed by the disadvantages of excessive drug costs that burden public health budgets and consumers, and fosters the corruption of doctors (Buckley, 2004).¹⁰⁹ Given the increasing propensity of drug companies to invest more in marketing at the cost of R&D (Gagnon and Lexchin, 2008, p. 32),¹¹⁰ scholars have advocated the institution of an independent informational resource (about medicines and treatment options for consumers and doctors) in lieu of advertising by drug companies (Bell *et al.*, 2000, p. 125).¹¹¹

Notwithstanding the above methodology, an objective determination of true costs will prove contentious and entail not so insignificant administrative costs, an aspect dealt with in detail later.

Submission of Information Relating to Profits

Apart from a mandatory submission of costs, pharmaceutical firms that opt to protect their investments under the proposed regime are required to submit their annual revenues and profits. These submissions enable a computation of returns year after year until such time as a drug originator recovers its costs and an appropriate rate of return on investment depending *inter alia* on the health impact of the drug.

In order that competing firms might monitor the effective period of exclusivity resulting from the operation of this model, and prepare for launching their generic versions, the following mechanism is proposed.

When the total profits earned by a drug originator come close to the costs incurred in relation to that drug, the originator must begin submitting a monthly account of its profits. Any follow-on manufacturer is permitted to file an application for regulatory approval of their generic version even prior to the expiry of the effective exclusivity period, and such approval can be granted, if the requisite regulatory standards are met. However, the competitor cannot launch its drug till such time as the exclusivity expires.

Although ascertaining costs and the profits of pharmaceutical firms in an objectively determinate manner is a difficult task and may be subject to manipulation in the initial years, it can be expected that after the regime has operated for some years, it will engender a more accurate evaluation of costs and revenue figures, an aspect dealt with more elaborately later in this section.

The Investment Protection Regime in Operation

The operation of the investment protection regime is best exemplified through the following illustration.

Assume that “X”, a pharmaceutical firm, obtains regulatory approval for drug “A” in the United States. The total cost of discovery and development of the drug up to the time of approval is USD 800.

Under the proposed regime, X is to be granted a legal monopoly (exclusivity in the market) till it recovers this amount, as also an appropriate rate of return, based on a “CoC” rate of interest and an additional rate based on the health impact of the drug.

The CoC of an investment is defined as the “rate of return that investors must be able to expect from money invested with a given level of risk” [Office of Technology Assessment (OTA), 1993, p. 48]. For pharmaceutical companies, it is the “opportunity cost” for being “tied up” in the discovery and development of a new drug (OTA, 1993, pp. 47–8). Therefore, pharmaceutical companies must not only be able to recoup “their actual cash outlays for R&D but also to be compensated for the risk they took of losing their investment altogether and for the time they spent waiting for the investment to pay off. Without such an expectation, no investor would put his or her money on the line” (OTA, 1993, p. 47).

There are two popular methods of calculating the “CoC” (Harrington, 2012, p. 76), namely the Capital Asset Pricing Model (CAPM) and the Fama–French (F–F) model (Fama and French, 1993). While the CAPM uses a single market risk factor (beta; Harrington, 2012, p. 2), the F–F model uses two other market risk factors, viz., a factor related to size of the firm and one related to the firm’s book-to-market equity (Fama and French, 1993, pp. 3–4; Harrington, 2012). A number of studies have used the CAPM in estimating the CoC of drug development.¹¹² Illustratively, the DiMasi study (DiMasi *et al.*, 2003) uses the CAPM in estimating CoC (DiMasi *et al.*, 2003, p. 163). The nominal CoC for the pharmaceutical industry in the period between 1995 and 2000 was estimated at 15% (real CoC after factoring in inflation was 11.9%; DiMasi *et al.*, 2003, p. 164). Observing that single factor models such as the CAPM can lead to underestimation of CoC for biotech and pharmaceutical firms, since they do not account for all types of systemic risks, Joseph Golec and John Vernon have used the F–F model in estimating the CoC in the biotechnology industry (Golec and Vernon, 2007). Their estimated average nominal CoC for pharmaceutical firms for 1985–2005 was 14.5%, whereas that for biotechnology firms for the same period was 16.25% (Golec and Vernon, 2007, p. 16).

The practice of including CoC as part of the total costs associated with drug discovery and development has been criticized by scholars such as Donald Light, who argues that the cost incurred by innovative firms in R&D is a regular cost of doing business and “estimated profits foregone should not be added to out-of-pocket costs at all” (Light and Wallburton, 2011, p. 8; Public Citizen, 2010).¹¹³

While one might debate the precise percentage of return that ought to constitute an appropriate CoC, ignoring these notional costs altogether may not be appropriate, given the real world in which investment risks in drug development are undertaken. If our financial markets guarantee a minimum rate of return to investors who simply park their money without doing more, drug originators that undertake significant risks in the hope of discovering a new drug deserve better than this.

Let us assume that the CoC rate of return is 10%. Let us also assume that the health impact of the drug merits a rate of return on investment amounting to 15%. The total rate of return on investment for that particular drug is therefore, 25%. The investment protection model has to therefore operate until X makes USD 1,000 (800 + the 25% rate of return).

It is pertinent to note that USD 1,000 is a hypothetical figure that is used to merely illustrate the working of the model. As will be shown in later parts of this section, the actual costs (to be finally recovered) are likely to be higher than this figure for the following reasons.

- (1) The costs of the drug would vary year after year (depending on the prospect of new drug approvals in additional countries where the drug is to be marketed).
- (2) The health impact is susceptible to variation in future years.
- (3) The rates of return would have to be added on year after year to the initial interest computed in the first year till such time as the drug originator is fully compensated under the model.
- (4) The USD 800 figure is a cost that occurs across a number of years. And if the costs of capital have to be meaningfully provided, then one might need to apportion USD 800 across the number of years over which the spending takes place and add the appropriate costs of capital each year.

Measuring Health Impact

Under the investment protection regime advocated in this article, the appropriate rate of return on investment depends upon the health impact of a drug. Two of the most prominent metrics that measure health impact areas follows:

- (1) QALYs.
- (2) DALYs.

Both QALYs and DALYs are economic tools for assessing the relative worth of health care interventions while making funding decisions (Acharya and Murray, 1997; Brower, 2008, p. 48). They express health in terms of time (life years) and attribute differential weights to diseases, depending on their impact on patients. In the terminology of Fryback *et al.*, both measures are health-adjusted life years (hereinafter “HALYs”; Fryback *et al.*, 2002).

A comprehensive discussion of these metrics is beyond the scope of this article. Although they come with their fair share of criticism (Harris, 2005; Harris, 1987, p. 119), the usage of such metrics is likely to yield a better outcome than the present patent reward structure which incentivizes a variant of Viagra to the same extent as it does a tuberculosis (TB) drug. Further, with increased usage, it can be expected that these metrics will evolve to more nuanced formats in the future.

A National Regime with an International Flavour

A national model of investment protection is one where the costs of new drugs are computed separately for each country and an exclusive period of protection is guaranteed in each country until such time that the profits earned in that country equal the costs incurred. However, in order to be equitable and effective, such a model must necessarily assume an international flavour, particularly in relation to the computation of costs.

It is illogical to apportion the entire costs of drug discovery and development to a single country, merely because the drug regulatory approval was first obtained in that country. Most drugs are developed for global markets; therefore, an equitable model would entail that the costs of drug discovery and development be apportioned between the various countries.

I propose a regime where the total global costs of drug discovery and development for any new drug, including the costs of all regulatory approvals are computed annually and apportioned between the various countries, depending upon the market share of the new drug in each country. This is further elaborated upon as follows:

Let us assume that “*X*”, a drug originator, obtains its first regulatory approval for a new drug in the United States. The total costs of drug discovery and development for the drug up to its time of approval is USD 500. The additional cost of obtaining approval in Europe is USD 200 and in Japan, USD 100. Under the model proposed in this article, *X* is to recover this amount (USD 800), as also a rate of return on investment corresponding to the CoC, and additionally, a rate of return on investment commensurate with the health impact of the drug. Let us assume that these rates of return add up to 25%. Therefore, the investment protection regime would need to work until *X* makes USD 1,000 (USD 800 + the 25% rate of return). This figure of USD 1,000 is subject to the earlier caveat, that the amount to be finally recovered will be in excess of USD 1,000 (since the returns add up each year etc.).

Assume that *X* earns USD 100 from the sale of the new drug in the United States in a certain year. Let us label this as $X(r_u)$. *X* earns USD 50 for a similar time frame in Europe ($X(r_e)$) and USD 50 in Japan ($X(r_j)$). The total worldwide revenue for that year is, therefore, USD 200. I now apportion the costs of drug discovery and development between the different countries, depending upon the proportion of sales of the drug in each country for that year. Thus, the proportion of the costs that

the United States has to bear is 50% (100/200), that is, USD 500. Similarly, Europe and Japan would each have to bear 25% of the costs, that is, USD 250 each. The investment protection regime operates in each of these countries in such a way that the period of exclusivity lasts till such time as the costs specific to that country are recovered.

It bears noting that the health impact of new drugs is likely to vary from country to country, depending upon the genetic profile of patients. Therefore, one has to take into account the average of the total health impact value for all countries where the drug is sold in a particular year. States can either insist on a local determination of health impact (in cases where state authorities are vested with the power to make such determinations) or rely on such determinations from other countries where the genetic profiles are largely similar. Further, the health impact value may change with time, as more information on the drug and its impact on patients emerge. The impact value of the drug, therefore, ought to be reassessed each year.

An alternative is to constitute a global agency tasked with assessing the average of the total health value and refining it year after year as more information on the drug becomes available. Such an agency could also be required to collate information on the costs and income of drugs annually. It bears noting that the costs, associated with drug discovery and development, are also subject to variation each year, depending on the pursuit of drug regulatory approvals in additional countries. Such costs associated with new drug regulatory applications ought to constitute a part of the total drug development costs. Further, the drug originator may also conduct additional trials in such countries to obtain regulatory approval. Therefore, the costs of the new drug ought to be recalibrated each year.

Operation of Exclusivity

Unlike standard data exclusivity regimes, the market exclusivity granted by the proposed investment protection regime is not tied-in to regulatory data in any manner. The regime offers absolute protection against follow-on entrants, in that even if competitors desire to conduct their own clinical trials and enter the market with a generic version of the drug, they cannot. To this extent, the model recommended is similar to the exclusivity associated with orphan drugs.¹¹⁴

Complete “market exclusivity”, as opposed to mere “data exclusivity” effectively means that no follow-on manufacturer can make or sell a drug containing an active ingredient that is the same or similar to the one under protection. The issue of “similarity” can be highly contentious, particularly in the context of biologics, where even a small change in protein structure can have a significant bearing on efficacy and toxicity (Levitt and Kelsey, 1993, p. 527).¹¹⁵

The latest FDA guidelines suggest that a follow-on molecule would be considered “different”, if it showed itself to be “clinically superior” to the known version under ODA protection.¹¹⁶ Clinical superiority is defined as “a significant therapeutic advantage over and above that provided by an approved orphan drug”.¹¹⁷ Therapeutic advantage¹¹⁸ can be demonstrated in one of three ways: (1) greater effectiveness; (2) greater safety or (3) a demonstration that the drug makes a major contribution to patient care in “unusual cases”.

Much in line with the above, it is proposed, that under the investment protection regime advocated in this article, “newness” (or “sameness”) be construed such that only a significant difference in therapeutic efficacy of a later drug ought to cause it to be treated as “different” from the originator drug and therefore outside the scope of the granted exclusivity.

Potential Abuse of Monopoly

As with all market exclusivities, the key disadvantage of a standard exclusivity-based investment protection regime is that it is likely to subject the market to the dictates of a single firm. This, in turn,

it is likely to engender high monopoly prices, deadweight losses and consequent loss of consumer welfare (Landes and Posner, 2003, pp. 17–20).

A recent example is “Makena”, a drug based on an existing form of a hormone (progesterone), titled “17P” and used to reduce the risk of pre-term births. The said hormone had been available for many years from compounding pharmacies for a price as low as USD 10.

KV Pharmaceuticals conducted trials on the drug, obtained FDA approval and began selling its version as Makena. It claimed that the trials were necessitated owing to apprehensions of purity and consistency in the quality of the drug obtained through compounding pharmacies. The approval of Makena gave KV Pharmaceuticals 7 years of exclusive rights under the ODA, subsequent to which it priced the drug at about USD 1,500 per shot; an increase of 14,900%, when compared with the equivalent drug obtained from compounding pharmacies (Staton, 2011).

The pharmaceutical company issued “cease and desist” letters to pharmacies, warning them that they could no longer sell their versions of drug (Pasquale, 2011). In the wake of widespread protests against such price gouging, the FDA clarified that it “does not intend to take enforcement action against pharmacies that compound 17P, in order to support access to this important drug” (FDA, 2011d).

Apart from the threat of excessive pricing, market exclusivities have the potential of creating an undersupplied market. Illustratively, during the bird flu outbreak, apprehensions were raised about Roche’s ability to adequately supply the Tamiflu vaccine to all parts of the world that required it (Amin and Basheer, 2006).¹¹⁹ Roche expressed its intention to remain the sole producer of Tamiflu (Amin and Basheer, 2006). Subsequently, owing to widespread protests and threats of compulsory licencing, Roche committed, in principle, to a wide licencing scheme so as to facilitate adequate and timely supplies in the event of a likely pandemic (Financial Express, 2005).

Compulsory Licencing

Since compulsory licences are powerful *ex post* tools that foster higher levels of competition, reduce prices and increase supplies, an investment protection regime with an inbuilt compulsory licencing model is preferable to a pure market exclusivity model. One might also consider price controls; however, such controls may have fewer advantages when compared with a robust compulsory licencing scheme. For one, unlike a price control regime, which has to necessarily fix an appropriate price for the drug in question, a compulsory licencing scheme could leave it to follow-on competitors to enter the market and drive down prices.¹²⁰

Secondly, a drug originator that is averse to a “controlled” price could simply opt out of the market, causing great harm to patients requiring the drug. Contrast this with a compulsory licencing regime, where follow-on competitors can manufacture and sell the drug irrespective of whether or not the drug originator is itself operating in the market (Lanjouw, 2003, pp. 112–15). Thirdly, a compulsory licencing regime enables generic manufacturers to acquire technological proficiency by offering them the freedom to legally copy a wider range of drugs. Fourthly, multiple follow-on drug manufacturers ensure that the market is adequately supplied at all times, which might not be the case if a market is subject to the whims of only one manufacturer, protected through a legally conferred monopoly (Fauver, 1988, pp. 668–74).

When considering a compulsory licencing scheme, one might think of two alternatives. The first is to formulate a compulsory licencing regime based on specific grounds or preconditions, as is the case with a number of patent regimes today. Illustratively, §84 of the Indian Patents Act 1970 stipulates that a compulsory licence could issue on the following grounds:¹²¹

- (1) that the reasonable requirements of the public with respect to the patented invention have not been satisfied, or

- (2) that the patented invention is not available to the public at a reasonably affordable price, or
- (3) that the patented invention is not worked in the territory of India.

Alternatively, countries could institute a blanket compulsory licencing or compensatory liability regime, where no market exclusivity is granted in favour of the drug originator, but merely the right to claim compensation from follow-on entrants. The term “blanket” refers to a compulsory licencing scheme available as a matter of right to an interested party, without the need to demonstrate the existence of specific grounds such as excessive pricing by the drug originator.

I propose both alternatives, and leave it to states to make this determination depending on their national technological capabilities and preferences. Developing countries with a reasonably strong generic industry, such as India, may wish to activate a blanket compensatory liability model in order to boost the competitiveness of its generic industry and ensure the availability of low-cost drugs to its patients (Basheer and Primi, 2009).

Under a compulsory licencing or compensatory liability model, the originator gains some level of protection, as the market entry of follow-on manufacturers is not “free”, but based on a compensation to be paid to the originator. Such a model provides fair protection to data originators, while at the same time preserving some amount of generic competition in the market, and helping reduce the prices to be paid consumers. Drug prices under such a model are expected to be higher than what might have prevailed in a completely free market scenario with no barriers to entry, since generic manufacturers need to compensate the drug originator and will likely pass on such costs to the consumer. Further, determining an appropriate quantum of compensation will entail administrative costs.

I use the term compulsory licencing to refer to a regime where follow-on innovators can enter the market only upon the occurrence of certain specified grounds (such as lack of adequate supplies or excessive pricing by the drug originator) and compensatory liability to refer to a more broad based framework, where follow-on entrants have the right to enter the market on the payment of reasonable compensation, without the need to show the existence of any specified grounds.

Whether one selects the first alternative (compulsory licencing triggered upon the existence of certain grounds) or a more broad based compensatory liability model that is near automatic in its operation, the key challenge is in determining the reasonable compensation to be paid by follow-on innovators. In the next section, I discuss existing models of compensation and then proceed to advocate what I believe to be a better methodology of compensation.

Compensatory Liability and Computation Methodology

A compensatory liability regime is not a new idea, but has been proposed and implemented in different forms.¹²² I discuss the most prevalent models below and focus in particular on the compensation methodology. I subsequently discuss the shortcomings of existing models and recommend a better methodology of computing compensation.

FIFRA

Under the US Federal Insecticide, Fungicide and Rodenticide Act (hereinafter “FIFRA”),¹²³ pesticides with new active ingredients, registered after 1978, are granted a 10-year exclusivity period.¹²⁴ After this period, the data can be “relied” upon for the next 5 years by follow-on entrants who have to adequately compensate the pesticide originator (Coll, 1986, p. 199).¹²⁵

The compensatory amount has to be voluntarily agreed upon by the parties, failing which it is referred to arbitration.¹²⁶ FIFRA does not set forth any explicit standard to compute “adequate remuneration”. While some suggest that this ought to be “cost” based, others argue that it be “value” based (Coll, 1986). A cost-based approach denotes an equitable sharing of the actual cost

of producing test data. This sharing could be done on a per capita basis, where the costs are divided equally between the originator and all subsequent follow-on entrants, or on a market share basis, where the costs are shared in a manner proportionate to the respective market share of follow-on entrants (Coll, 1986, p. 194).

Value-based compensation, on the other hand, compensates an originator based on the “value” derived by a follow-on entrant who, by virtue of its reliance on the originator data, is able to enter the market at an earlier point in time.¹²⁷

Given that a number of arbitral awards are not accessible to the public, one is unable to review such orders and evaluate the compensation methodology adopted. Even assuming that FIFRA computations were to be based on a clear “cost sharing” model, a simplistic per capita model, though relatively easy to operate, would not be fair. Firstly, follow-on generic entrants may not have deep pockets to share the entire costs of data generation upfront in the first year of entry. Secondly, the model does not admit of easy computation, when further follow-on entrants enter the market. Assume that “*A*” is the originator and “*B*” is the first generic or follow-on entrant who pays 50% in the first year of entry. If a subsequent competitor, “*C*”, enters the market in the second year, would the burden have to be split so that *B* and *C* each bear 33.3% of *A*’s cost? And would *A* have to return 16.7% to *B*? Thirdly, the percentage of costs to be paid by each generic entrant ought to have some co-relation with the benefits of market access. In other words, generic entrants ought to share only to the extent of their respective market shares.

Fellmeth Model

Aaron Fellmeth advocates a sophisticated cost-sharing model in the form of “re-adjustable royalties” (Fellmeth, 2004, p. 482). As the name suggests, the royalties to be paid by each generic entrant (labelled as “subsequent applicant” by Fellmeth) depends upon the total number of applicants each year and it varies (readjusts) each year upon the entry of new players.

Given that the first generic entrant enjoys the potential for maximal market access (compared with other subsequent entrants), Fellmeth proposes that this first-mover should pay the highest proportion of costs (computed as a percentage of the total originator costs), which can be fixed at any given percentage. Similarly, the first few entrants who enter the market would have to pay more than those that enter the market in the later years and enjoy a correspondingly lower market access. In order to compute the precise percentage of compensation that subsequent entrants have to pay, Fellmeth proposes a formula as follows (Dinca, 2005, p. 555) :

$$g = [a + 0.01(b - 1)]/b,$$

where *g* is the annual percentage to be paid by each subsequent applicant; *a* is the fixed annual percentage to be paid by the first subsequent registrant and *b* represents the total number of registrants.

The percentage amount recovered by the originator from a subsequent entrant who pays an annual percentage of *g* would be:

$$t = bge,$$

where *t* is the originator’s recovery and *e* is the duration of protection expressed in years.

While the Fellmeth model is certainly an improvement over the simple equitable cost division model (Fellmeth, 2004, p. 482), it suffers from certain serious drawbacks. Firstly, it assumes that the first few entrants would have more access than subsequent ones. It could well be the case that subsequent entrants capture more of the market than earlier ones. Further, even with respect to follow-on firms, which enter the market at the same time, some may capture a higher percentage of the market than others.

Secondly, the Fellmeth model stipulates an arbitrary percentage to be paid by the first generic entrant (Dinca, 2005, p. 557). Dinca takes issue with the Fellmeth model for the above reasons (Dinca, 2005, p. 557). He demonstrates that despite Fellmeth's promise, subsequent generic entrants could end up paying more than the first entrant. Dinca hypothetically fixes the percentage of compensation that the first generic applicant has to pay at 0.5 and shows that the second applicant in the second year ends up paying a higher figure than the first applicant in the first year.

Dinca Model

In order to address the various deficiencies in the Fellmeth model, Dinca proposes that compensation be computed as under (Dinca, 2005, p. 557):

$$s = [C(1 + i)]/[t(n + 1)],$$

where s is the compensation paid by each generic entrant, C the total costs incurred by the originator in creating the data, i the average banking interest rate for the year, t the number of years in the protection period and n the number of generic applicants who wish to use the data that year. The compensation received by the originator in a particular year would be ns , that is, the product of the number of generic applicants and the compensation to be paid by each such applicant (Dinca, 2005, p. 558).

The following example is illustrative. Assume that the cost incurred by an originator "O" in generating regulatory data is USD 100 and the period of protection under the national law is 5 years. The average bank rate of interest is 10% per annum. The compensation to be paid out by the first generic entrant "A" who wishes to rely on originator data, and enter the market in the year following the year in which the drug is first introduced by the originator would be:

$$s = [C(1 + i)]/[t(n + 1)] = 100(1 + 10/100)/5 \times 2 = 11.$$

Let us now assume that two more generic applicants ("B" and "C") wish to enter the market a year after A's entry. The compensation that each such subsequent entrant ought to pay is as follows:

$$s = 100 \times 1.1/5 \times 4 = 5.5.$$

At the end of 5 years of operating the model, the costs paid out by each generic entrant would be as follows:

$$A = \text{USD } 27.5 \text{ (USD } 11 + \text{USD } 16.5 \text{ (USD } 5.5 \times 3 \text{ years))}$$

$$B = \text{USD } 16.5$$

$$C = \text{USD } 16.5.$$

The contributions would add up to a total of USD 60.5. The originator would, therefore, have to bear USD 39.5 of the total cost of USD 100.

While Dinca's model is an improvement over the Fellmeth model, it suffers from the following drawbacks:

- (1) It assigns an arbitrary time value in that Dinca suggests that the model should compensate for t number of years, without elaborating on why one must pick a variable such as t in the first place at all (Dinca, 2005, 560).¹²⁸

- (2) As with Fellmeth, Dinca fails to consider the specific market share of the each follow-on generic entrant. Under his model, an entrant who captures only 10% of the market in a certain year would have to pay the same amount of compensation as another entrant who captures 50% of the market in that year.

Standard Royalty Model

Apart from the above, one might consider a standard royalty model, as that proposed by Reichman:

... a simpler approach may prove more desirable, if only to avoid litigation and other transaction costs. On this approach, a reasonable royalty model could be adopted instead, which would oblige generic producers to pay a flat percentage of gross sales, or a flat percentage above marginal costs of production, as the right to rely on the originators' test data results for a specified period of time, to last no longer than five years ... (Reichman, 2009, p. 35).

Although such a model may be easier to operate, the flat rate suggested,¹²⁹ as also the number of years of protection (5 years) are both arbitrary figures (Orlhac, 1990, p. 4),¹³⁰ in much the same way as Fellmeth's initial royalty rate¹³¹ and Dinca's fixed time period of protection.¹³²

Novel Methodology of Compensation

In order to provide for a more equitable solution than the models discussed above, I propose that follow-on market entrants only pay an amount commensurate with their market share. Further, in order to ensure that the compensatory amounts paid out do not render market entry unprofitable, I propose that they be made to pay only a certain proportion of their profits, and not their overall revenues. Lastly, the key advantage of this model is that it does not stipulate any arbitrary time period of protection. Rather, the model operates until such time as the costs along with an appropriate rate of return on investment are recovered by the drug originator.

Consider the hypothetical case below, based significantly on the example cited in an earlier section "the investment protection regime in operation". Assume that "X", a pharmaceutical originator firm obtains its first regulatory approval in the US on March 1, 2010. The total costs of drug discovery and development for the drug in question up to the time of approval in the United States is USD 800.

Under the proposed regime, X is to recover this amount, as also an appropriate rate of interest based on costs of capital, and a rate of return on investment based on the health impact of the drug. Let us peg the CoC rate of interest at 10%. Let us also assume that the health impact of the drug merits a 15% rate of return. The total rate of return on investment for the first year that the drug is introduced in the market is therefore, 25%. The compensatory liability model would need to work until X makes USD 1,000 (800 + the 25% rate of return). As noted earlier, this figure of USD 1,000 is subject to the caveat, that the rate of return for each year would vary and would have to be added on to the original returns in the first year. To this extent, the final compensable amount will be in excess of USD 1,000 (since the returns add up each year).

Let us assume that X earns a profit of USD 100 in the United States in the first year of the drug being sold (March 1, 2010 to March 1, 2011). Let us call this profit $X(p)$. A generic entrant "Y" also enters the market very close to X's entry. Y's profits $Y(p)$ from the sale of the drug for that year is USD 50. I apportion the costs that Y would have to pay X in a manner proportionate to the market access of Y relative to X. I calculate market access on the basis of total revenues earned by each market entrant in a certain year. Let us assume that Y earns USD 100 ($Y(r)$) and that X earns revenue of USD 200 ($X(r)$) for the period above-mentioned (March 2010 to March 2011). Given that $Y(r)$ is one-third of ($Y(r) + X(r)$), Y would have to pay one-third of its profits $Y(p)$ for that year as compensation to

X , that is, approximately USD 16.67. I label this figure as $Y(c)$. If another generic entrant “ Z ” enters the next year, it would have to pay $Z(c)$ to X , in accordance with the above formula.

However, we need to take into account X 's profits as well from the sales of the drug. Let us assume this is $X(p)$. Therefore, each year, the total compensation (recovery of investments) flowing to X would be computed, thus:

$$A = X(p) + Y(c) + Z(c).$$

Once the total compensation accruing to X reaches the sum of USD 1,000, the model stops operating and subsequently any firm is permitted to enter the market without paying any compensation whatsoever.

Since follow-on entrants are likely to commence their market operations at different times throughout the year, it is necessary to have a cut-off for computing the compensation due each year. Let us fix this cut-off as the first day of March each year. If a generic firm enters the market in January of a certain year, I compute the profits made up to the start of March and then compute the cost (in terms of its market share) that it needs to pay. Thus, if it earns only USD 10 in the first 2 months of its market entry and has a resulting market share of only 1%, it will have to pay 1% of its profits. However, for the purpose of ease of operation of the model, it could be stipulated that no follow-on entrant could enter the market after February 1 for that year. Competitors ought to make payments within a few months of the date of final computation. Assuming the administrative authority procures all relevant data and is able to arrive at the amount of compensation due by the start of April, firms could be asked to pay within the next 2–3 months.

An International Flavour

The compensatory investment protection regime as discussed above is to work separately in each jurisdiction; such that only costs specific to that jurisdiction are considered and compensated for. However, as noted earlier, it is arbitrary to attribute drug discovery and developmental costs to any particular country. An optimal regime is one that computes the global costs each year and then apportions them in a manner commensurate with market share of the drug in each country, as detailed below. To this extent, the proposed regime ought to be based on certain common international norms (relating to computation of costs and the like) that member states agree to implement domestically.

Assume that “ X ”, a pharmaceutical originator firm obtains its first regulatory approval in the United States on March 1, 2009. The total costs of drug discovery and development for the drug in question up to this time of approval in the United States is USD 500. The additional cost of obtaining approval in Europe is USD 200 and Japan, USD 100. Under the model proposed in this article, X would recover this amount (USD 800), as also a rate of return on investment. Let us assume that this rate of return is 25%. Therefore, the compensatory liability model would need to work until X makes USD 1,000 (800 + the 25% rate of return).

Assume that X earns USD 100 in the United States in the first year of the drug being sold (March 1, 2009 to March 1, 2010). Let us label this as $X(r_u)$. X earns USD 50 for a similar time frame in Europe ($X(r_e)$) and USD 50 in Japan ($X(r_j)$). The total worldwide revenues earned for that year are, therefore, USD 200. I now apportion the costs of drug discovery and development between the different countries, depending upon the proportion of sales in each country for that year. Thus, the proportion of the costs that the United States has to bear is 50% (100/200), that is, USD 500. Similarly Europe and Japan would each have to bear 25% of the costs, that is, USD 250 each.

Once this relative national cost is computed, the model would operate in much the same way as earlier discussed. Assume that a generic entrant “ Y ” enters the US market at a time very close to

X 's entry. Y 's profits $Y(pu)$ from the sale of the drug for that year in the United States is USD 50. I apportion the costs that Y would have to pay X in a manner proportionate to the market access of Y relative to X . Assuming that $Y(ru)$ is one-third of $X(ru) + Y(ru)$ (as from the earlier example), Y would ordinarily have to pay one-third of the total amount of its profits to X within the United States. I label this figure as $Y(cu)$. It may then have to pay a different compensation amount in Europe and Japan ($Y(ce)$ and $Y(cj)$, respectively), depending on

- (1) its date of entry into the Europe and Japanese markets;
- (2) the proportionate cost of drug approval in the Europe and Japan (computed as a proportion of Y 's revenues in Europe and Japan, relative to that of X) and
- (3) the profits made by Y relative to those made by X in the European and Japanese markets.

If another generic entrant “ Z ” enters that year, Z would pay $Z(cu)$, $Z(ce)$ and $Z(cj)$ assuming it enters all three markets.

Each year, the total compensatory amount A flowing to X is computed as follows:

$$A = X(pu + pe + pj) + Y(cu + ce + cj) + Z(cu + ce + cj).$$

This model continues year after year until the cumulative compensation accruing to X reaches USD 1,000. As noted earlier, the figure of USD 1,000 is a hypothetical one; owing to additional interest paid out each year as also the varying rates of return each year, the amount to be compensated will be higher than USD 1,000. Also, drug originator costs have to be recalculated each year, since it is possible that additional regulatory approvals are procured in new countries.

In conclusion, a compensatory liability regime encourages more competition and drives down prices and is, therefore, more advantageous from a patient and public health perspective, when compared to a pure market exclusivity model. I advocate a model of compensation, which avoids the shortcomings of earlier models and makes for a fair and equitable model. However, the efficacy of the regime depends, to a significant extent on the accuracy of figures submitted by each of the parties (costs of R&D, as also the revenues and profits made by the originator and generic competitors year after year). The model is likely to involve administrative costs and the figures are likely to be heavily contested in the initial years of operation (Lemley and Weiser, 2007).¹³³

Reimbursement Model

Apart from the models discussed above, a drug originator could also have its investments reimbursed through public funding or prizes. For the purpose of this article, the term “reimbursement” includes within its ambit both the R&D investment and an appropriate rate of return on that investment, depending on the costs of capital and the health impact of the drug. Absent this rate of return, a drug originator has reduced incentive to pursue drug discovery, since it would merely recoup its costs, while its competitors gain easy market access, leaving it with no additional advantage and financial incentive.

Public funding: A number of commentators have advocated for the public funding of drug discovery and development. James Love notes:

[G]overnments could expand direct funding for drug development, either through the existing structures such as the NIH collaborations with industry and academia, or through non-profit development projects, such as those currently resourced to address treatments for neglected diseases like malaria and TB (Love, 2003).¹³⁴

In particular, scholars recommend that clinical trials (the most expensive part of drug discovery and development) be publicly funded owing to the potential for bias arising from corporate sponsorship. In a persuasive paper, Tracy Lewis *et al.* (2007) propose that clinical trials be undertaken by a neutral public funded body with no links to the pharmaceutical industry or any other person with a direct stake in the drug under testing.¹³⁵

For the purpose of this article, any such public funding must be in the nature of an “ex post” reimbursement, that is, reimbursement after the investments have already been made by a drug originator. Secondly, it must cover all “investments” associated with the drug in question (including costs associated with failure) as already outlined earlier in this section. It bears noting that although public funding of R&D is common in several countries, it is often not comprehensive enough to fund the entire process of drug discovery and development (European Medical Research Councils (EMRC), 2007, pp. 16–9; Moses III *et al.*, 2005; United States Senate, 2000).¹³⁶

Such public funding of the investment costs could be operationalized through a direct transfer of funds from the government to the drug originator or through instruments such as tax credits, where the tax liability of the drug originator is reduced to the extent of the amount offered as the credit.¹³⁷

A number of countries offer tax credits with a view to encouraging investment in R&D (Deloitte, 2011).¹³⁸ Illustratively, the United States provides an Orphan Drug Tax Credit, where, a firm is entitled to claim a 50% tax credit for expenditure on human trials for orphan drugs.¹³⁹ Similarly, the United Kingdom provides tax credits for investments in vaccine and R&D for diseases such as HIV/AIDS, TB and malaria.¹⁴⁰ Such credits have largely helped increase investments in R&D (Bloom *et al.*, 2002, p. 21; Czarnitzki *et al.*, 2004, p. 21; Hall and Reenen, 2000, p. 462).¹⁴¹ However, the regime has not been without its fair share of criticisms, the most pertinent of which is that it incentivizes firms to use creative accounting to maximize their tax claims, (Hall and Reenen, 2000, p. 263)¹⁴² a concern dealt with later in this section. Further, tax credits work as an incentive only if the firm has significant enough taxable profits that can be offset with the help of such credits (Hall and Reenen, 2000, p. 456).¹⁴³

Prizes: The system of prizes/rewards predates the patent system and has been advocated by many scholars as a more optimal incentive (Hubbard and Love, 2009, p. 175).¹⁴⁴ Distilled to its bare essence, a prize entails a sponsor announcing a reward for a specific kind of innovation and then proceeding to make good the promised reward to any person/entity that comes up with the relevant innovation. Prized could be offered by any agency or entity, be it the government (in which case it would qualify as a kind of public funding) or any private party.

In the context of pharmaceutical innovation, the Health Impact Fund (hereinafter “HIF”) is a good example of a prize, where drug innovators are rewarded based on the therapeutic value of their products through a government sponsored fund (Hollis, 2005).

The HIF rewards new drug originators by paying them a pre-defined number of years, for example, a new pharmaceutical product might earn payments from the HIF every year for its first 10 years of use (Hollis, 2008, p. 127). In this respect, the HIF differs from a patent buy-out, in that the drug originator continues to own the intellectual property, but agrees to desist from charging a monopoly price. Instead, the drugs have to be sold globally at no more than the lowest feasible cost of production and distribution (HIF, 2012).

Any new drug originator is entitled to register with the HIF and stake a claim for a portion of the fund. Such registration requires the drug firm to sell its product worldwide at an administered price near the average cost of production and distribution. The administered price is listed on the official HIF website, such that wholesale buyers are aware of it. Thus, the registrant retains exclusivity in the product, but foregoes the monopoly price in return for payments from the HIF. In exchange, the firm

receives a stream of payments from the HIF based on the relative incremental global health impact of its drug (Hollis and Pogge, 2008).

The key problem with the HIF model (as with any reimbursement model that depends on external funds) is that in order to work effectively, it requires a significant infusion of funds. The authors of the model recommend an annual funding of least USD 2 billion—USD 10 billion (Hollis, 2008, p. 129). In order to make the fund credible enough for firms to participate, the authors propose that countries commit substantial funding far into the future, at least for a minimum of 12 years (Hollis and Pogge, 2008, p. 10). A large part of the efficacy of this instrument therefore depends on the political will of governments (particularly those of developed countries) to contribute these significant sums of money year after year.¹⁴⁵

Secondly, while the HIF enables drug originators to recover their manufacturing costs, it is not clear if the rewards will fully cover R&D expenses (Hollis *et al.*, 2010, p. 183). There is no explicit reimbursement for the costs of R&D of the drug, and it is unclear whether these expenses are likely to be recovered by payments made out of the HIF. The amounts that are finally allotted to participating drug originators cannot be known in advance and depends on the fund availability at that point in time and the number of HIF registrants competing for the fund (Baker, 2008). This uncertainty is likely to cause drug originators to continue relying on the patent system and forego the opportunity of registering with the HIF.

Much like the compensatory liability model discussed earlier, the key advantage of a reimbursement model (either through public funding or prizes) is that it ensures that the drug is introduced in the market without any exclusivities, thereby fostering competition and lower prices. However, its key drawback is the fact that it depends for the funding on the government and other external agencies (Love, 2003).¹⁴⁶

Apart from the investment protection models considered above, there are other non-patent based regimes that have been proposed for incentivizing drug discovery and development, such as Advanced Purchase Commitments.¹⁴⁷ However, most such instruments have limited value, in that they are likely to be efficacious for a small number of drugs that cater to neglected diseases.

Electing Between Patents and Investment Protection

The investment protection regime advocated in this article compensates the drug originator comprehensively for expenses associated with drug discovery and development. Therefore, any additional patent protection for the drug originator over the same drug will lead to over-compensation. In order to reduce the scope for such over-compensation, it is recommended that the firm in question be forced to elect between the two regimes. If it chooses to retain its patent rights, it cannot avail of the proposed investment protection regime. Similarly, if it chooses to avail of the investment protection regime, it has to necessarily relinquish all patents covering the drug.¹⁴⁸

The key advantage of the investment protection regime over the patent system is that the former guarantees some amount of market protection, either through exclusivity, compensatory liability or through a reimbursement from public funds or prizes. A patent on the other hand remains susceptible to uncertainty, as the patent could be invalidated at any time in most countries. It is also possible that courts refuse injunctions to restrain infringers, but simply award damages after a prolonged trial.

On the other hand, a patent regime is advantageous to drug originators in that they are saved the trouble of having to submit sensitive cost data. Further, in some cases (depending on the patent term remaining after the drug is approved and marketed), it could enable the originator to gain a longer period of protection than an investment protection regime.

The HIF model, elaborated upon in earlier paragraphs¹⁴⁹ also advocates a similar election between the HIF fund and the patent system. As the authors of the model note, firms are likely to

elect the HIF fund only when they expect greater returns from the fund, when compared with an unconstrained use of patent exclusivity.¹⁵⁰

One might ask if the above election scheme is compatible with TRIPS. I argue that it is for the following reasons. Firstly, patents are not necessarily denied to a drug originator in violation of TRIPS. Rather, it is left up to the originators' discretion as to whether or not it wishes to forego this protection in favour of the investment protection regime.

While critiquing the current patent system and advocating for an incentive system based on prizes, Fisher and Syed (2008, p. 46) express a similar view i.e. a voluntary prize system that exists alongside the patent system is compatible with TRIPS as the drug originator is not denied patent protection but is choosing to eschew it in favour of the proposed prize model.

In the *Indonesia Autos* case,¹⁵¹ which dealt with the legality of tax and import duty exemptions on cars that met certain requirements under the "National Car Programme" (NCP), the United States claimed that Indonesia violated article 20 of TRIPS.¹⁵²

Under the programme, a trademark applicable to a "national motor vehicle", that is, a car that qualified for benefits under the programme had to be owned by an "Indonesian" company. The United States argued that if its companies entered into an arrangement with a Pioneer company (a domestic company manufacturing cars eligible for benefits under the NCP), it would be unlikely to additionally use the trademark it used globally on the car marketed as a "national motor vehicle" in order to avoid confusion resulting from the use of two marks on the same car.

To this extent, the United States argued that since it would be "encumbered" in using the trademark it normally used in other parts of the world, the Indonesian programme constituted a violation of article 20 of TRIPS, which required that

(t)he use of a trademark in the course of trade shall not be unjustifiably encumbered by special requirements, such as use with another trademark, use in a special form or use in a manner detrimental to its capability to distinguish the goods or services of one undertaking from those of other undertakings (TRIPS, article 20).

The panel however rejected this argument on the basis of the voluntary nature of programme, noting that "if a foreign company enters into an arrangement with a Pioneer company, it would do so voluntarily, with knowledge of any consequent implications for its ability to maintain pre-existing trademark rights . . ." ¹⁵³

The above ruling suggests that a "voluntary" arrangement wherein a drug originator is asked to choose between a TRIPS-mandated patent protection and an optional investment protection regime is not likely to violate article 27 or any other provision of TRIPS.

The Advantages of an Investment Protection Regime

When compared with a standard data exclusivity regime, the primary advantage of a comprehensive investment protection model is that it asks for the actual cost of discovery and development for each drug and grants a proportionate level of protection based. The regime is premised on the logic that while the investment may be recouped in a mere 2 years for some drugs, it could take up to 7 years for others. To this extent, it avoids both under compensating and over-compensating (NIH, 2008)¹⁵⁴ the drug originator.

The second advantage of the proposed regime is in terms of its potential to disincentivize the creation of evergreened or "me-too" drugs (Boldrin and Levine, 2005, p. 226).¹⁵⁵ The term "evergreening" is one with healthy overtones in the environmental sciences¹⁵⁶ but fairly pejorative when applied to the pharmaceutical industry (Thomas, 2009, p. 1).¹⁵⁷ As yet, there is no standard definition for this term; rather, its popular usage often refers loosely to a set of practices designed

to preserve market exclusivities by patenting derivatives, which often confer little or no advantage to the patient, when compared with the previous parent drug.¹⁵⁸

The *Prilosec v Nexium* case is illustrative of this phenomenon. As Astra Zeneca's patent over its anti-heart burn drug, "Omeprazole" (brand name, Prilosec) expired; it introduced an allegedly superior derivative, "Esomeprazole" (brand name, Nexium) (Swidey, 2002).¹⁵⁹ The active ingredient underlying Nexium was the same as that of Prilosec, the key difference being that while Prilosec was a racemic mixture, Nexium was one of the enantiomers that constituted the racemic mixture (Harris, 2002).

The investment protection model advocated in this article addresses the scourge of evergreening by stipulating that drugs merit a rate of return on investment proportionate to their health impact. If, as was the case with Nexium, the health impact of a drug is relatively insignificant when compared with its earlier known equivalent, it will merit only a miniscule rate of return on investment. Secondly, the costs associated with developing such an evergreened variety are likely to be far lower than that associated with discovering and developing the first in time drug (Prilosec). Therefore, the period of exclusivity associated with Nexium (even if approved by the regulator) is likely to be far lower than that associated with Prilosec.

Thirdly, even assuming a Nexium-type variant with relatively insignificant health impact were to be developed by another drug manufacturer and not necessarily Astra Zeneca, the investment protection regime proposed in this article would disincentivize such creations, as they protect the originator molecule from pure generic versions, as also from versions that are not the same, but only "similar" to the originator molecule.

In short, the investment protection regime advocated in this article effectively disincentivizes the creation of evergreened derivatives with insignificant health impact. The evaluation of health impact (which in turn determines the rate of return on investment) has to be made by the drug regulatory agency or any other authority at the time of drug approval. However, as noted earlier, the health impact value will be recalibrated during the time of operation of the drug, in the light of new and emerging evidence.

Fourthly, a significant advantage of the investment protection regime is that unlike existing data exclusivity regimes, it is not tied to regulatory data in any way. Rather, it includes the cost of regulatory data as well as upstream drug discovery investments. Fourthly, it provides a broader market exclusivity (than regular data exclusivity regimes), where a follow-on entrant cannot enter the market, even if it generates its own data. In other words, the drug originator can prevent any third party from entering the market, if such third party develops a drug or drug derivative that is not significantly clinically superior to that of the drug originator. To this extent, the proposed regime goes beyond protecting the originator against mere free riders.

In this context, it is important to appreciate that while data exclusivity regimes may be seen to have an "investment" inducing function, they are tied-in to the larger purpose of drug regulation, which is to ensure that drugs are safe and effective. To this extent, I propose that the investment protection models advocated in this article are better seen as stand-alone investment protection regimes, rather than as an amendment to any of the existing data exclusivity regimes. Such a comprehensive regime dispenses with the need to have a separate data exclusivity regime, barring special instances such as paediatric exclusivity, where additional trials on paediatric populations may need to be incentivized, after the drug has gained marketing approval.¹⁶⁰

Unlike patents, where an *ex ante* evaluation of the merits of an innovative product and a determination of an appropriate level of protection is difficult (Cornelli and Schankerman, 1999, p. 209), an investment protection regime is more amenable to such determination, as it requires individual costs and profits per drug. In order for the model to work, all drug companies that wish to benefit

from this scheme ought to submit their costs of drug discovery and development (as well as their yearly profits) to the relevant body tasked with administering this model. Risks of costs inflation and manipulation exist, but as noted earlier, this is likely to abate over time as the model matures in its working. An incidental advantage of the proposed model is that, over a period of time, one is likely to get a more accurate estimate of the average costs for drug discovery and development. Given the general reluctance of pharmaceutical firms to share such figures, the proposed model will promote more transparency and prove tremendously valuable in the long run. Lastly, in order to ensure greater transparency around clinical trial data, the proposed regime could also insist upon a public disclosure of all such data in order to merit investment protection.

The Disadvantages of an Investment Protection Regime

In view of the fact that accounting methodologies and costs associated with drug discovery and development remain contested to this day, the investment protection regime proposed in this article is likely to witness some amount of cost exaggeration from drug originators (Cordes, 1984, p. 11; Merges, 1992).¹⁶¹

Cost exaggeration through a variety of creative accounting techniques¹⁶² have been deployed in a wide variety of instances—the most famous being the Enron accounting scandal where a leading global energy corporation deliberately misled the public about its profits by concealing its debts in the company's accounts (Brown and Thapa, 2007).

Such inflation has also been witnessed in relation to tax credits; a study conducted by the US Congressional budget office in relation to tax credits claimed by drug originators notes: “[t]o take advantage of the favorable tax treatment of spending for research and development, firms have an incentive to classify as many expenses as possible as R&D related, an incentive that grows with the credit's generosity” (Congressional Budget Office, 2007, p. 24; Koh Jun, 2012, p. 4).¹⁶³

In order to reduce the prospects of cost exaggeration and over-compensation, an investment protection regime could include the following safeguards:

- (1) All cost estimates that are submitted to the relevant government authority have to be made public (Love *et al.*, 2006). This is likely to trigger objections from competitors and civil society members who may identify a deliberate inflation of costs or methodological flaws in the computation mechanism. In order to provide a more robust framework for such critique, one could devise a system similar to the patent opposition machinery, where third parties are invited to contest the computation through a speed and inexpensive administrative process.¹⁶⁴
- (2) Costs could be made mandatorily auditable by an independent certified third party, in accordance with internationally accepted accounting norms (Fellmeth, 2004, p. 495).
- (3) Costs could also be verified against R&D costs that are likely to be submitted to other regulatory authorities such as tax returns or filings claiming tax credits. A number of countries around the world offer such tax credits as incentives for investment in R&D (Deloitte, 2011). However, this comes with the caveat that the figures submitted for tax credits themselves may be inflated as noted earlier.
- (4) Lastly, one could also borrow from costing methodologies deployed in other legal regimes that seek to regulate the prices of drugs such as drug price regulations and competition law. Illustratively, in Belgium and Finland, the maximum price at which a drug can be sold is set with reference to a number of factors including R&D costs (Kanavos, 2001, p. 9; PhRMA, 2004, pp. 5, 14).¹⁶⁵

Similarly, European competition authorities engage in cost determinations while determining whether an undertaking has abused its dominant position by engaging in excessive or predatory pricing.¹⁶⁶

Notwithstanding the above safeguards, an objective determination of true costs will always prove difficult and contentious and likely involve significant operational costs. While the article acknowledges these difficulties, it also notes that it is likely to abate with time. In particular, government administrators of such a regime will, over time, become more adept at scrutinizing the veracity of submitted figures.

The objective of this article is not to yield a perfect model, if ever there was one;¹⁶⁷ rather, it is to advocate a regime that is at least relatively more optimal as an investment protection instrument than the current patent system, which is premised *inter alia* on a faulty uniform period of protection. Given that the patent regime seeks to foster innovation and creativity, it will be rather paradoxical if the regime itself were shielded from any innovative experimentation.

Patents, Upstream Inventions and Incentives

My central argument in this article is that an investment protection regime is far more optimal than either a patent regime or a data exclusivity regime in fostering higher levels of investment into drug discovery and development. I, therefore, propose that countries dispense with existing data exclusivity regimes.

However, what of the patent regime? Can countries forego this as well, in the specific context of pharmaceutical innovation? Part II explored the incentive theory rationale underlying the patent system and found that it lacks persuasive empirical support. Notwithstanding this shortcoming, countries cannot dispense with the patent system altogether, owing to the binding nature of TRIPS, under which they have to mandatorily provide a 20-year patent protection for all “inventions” that are new, useful and inventive.¹⁶⁸ However, TRIPS offers enough flexibility to member states to institute fairly rigorous patentability thresholds to ensure that only the most meritorious inventions make it through the filter.

The question then arises: would such rigorous patentability thresholds impact the rate of upstream pharmaceutical discoveries by third parties? I argue that there are significant non-patent incentives that could be availed of to ensure that upstream inventions (by third parties) continue without serious disincentive. Therefore patent standards for upstream inventions could be kept at fairly rigorous thresholds.

Upstream Inventions and Incentives

The current pharmaceutical innovation framework is such that the discoverer of the drug molecule¹⁶⁹ may not necessarily be the same as the entity that finally develops and markets the drug.¹⁷⁰ In other words, one cannot always assume that a drug originator is singularly responsible for the discovery and development of a drug (Crossman *et al.*, 2008).

There is considerable debate surrounding the number of new drugs that are based on upstream inventions attributable to third parties.¹⁷¹ A recent study indicates that approximately half of all drugs that were granted priority review (indicating thereby, that they catered to unmet medical needs) and approved by the US FDA during 1998–2007 emanated from small biotechnology firms or universities.¹⁷²

This trend is likely to accelerate in future and any model for incentivizing drug discovery and development ought to factor in this possibility, of upstream inventions being attributable to a party other than the final drug originator (Rasmussen, 2007, p. 4).¹⁷³ The rate of inventive output from such third parties depends to a large extent on the kind of incentives that exist at these upstream stages.

The sections “A New IND Right”, “Trade Secrecy” and “Publications, Reputational Gains and Collaborative Innovation” attempt to highlight the various incentives that exist for upstream third party research. One might consider the following alternative scenarios pertaining to upstream research:

- (1) where the upstream research is conducted by a public funded institution or entity;¹⁷⁴ and
- (2) where the upstream research is conducted by a private firm or entity.

In so far as scenario (1) is concerned, it is reasonable to expect that public funding will continue even in the absence of patents and recoverable licence fees (Outterson, 2008, p. 288).¹⁷⁵ Such funding, in most cases, is not contingent upon whether the money spent on research is recoverable financially through market monopolies and patents. Although the advent of regimes such as the US Bayh-Dole Act¹⁷⁶ may have changed this equation to some extent (Henderson and Smith, 2002, pp. 4–5; Raubitschek, 2005, pp. 313–4), it would be fair to state that public funding is not likely to wither away in the absence of patent protection for inventions ensuing from such funding.

A New IND Right

Private firms or institutions contributing to the drug discovery process may be reluctant to invest in R&D without some form of legal protection that helps recoup expensive investment. It bears reiteration that although the most significant component of the expenses associated with drug discovery and development are attributable to clinical trials, the process of drug discovery leading up to the filing of an investigative new drug application (INDA; FDA, 2011b)¹⁷⁷ or an equivalent CTA application in the EU (Foote and Wood, 2009)¹⁷⁸ also comes with significant expenditure and risk.¹⁷⁹

Some upstream entities are likely to possess the technological and the financial wherewithal to take a drug molecule up to the INDA or the CTA stage, but not to the clinical trial stage (Kneller, 2010; Su *et al.*, 2010, p. 4). I, therefore, propose a separate exclusivity right in favour of such entities, wherein the mere filing of an INDA or CTA triggers a right to claim reimbursement of all costs associated with the drug discovery up to the time of filing of the said INDA or CTA. However, such right is contingent upon the final approval of the drug in question by the regulatory authority. The proposed contingent right is elaborated upon as follows:

If an IND or CTA applicant does not choose to pursue the INDA and conduct clinical trials, it must make its intentions known to the drug regulator (FDA or EMEA). The IND or the CTA application is then thrown open to any interested third party to pursue, and the said party may apply to the FDA or EMEA to conduct human trials based upon the filed INDA/CTA.

If the said third-party firm achieves final drug regulatory approval, it ought to appropriately credit the INDA or CTA applicant. In this way, one might consider both the INDA/CTA applicant and the firm that finally obtains regulatory approval to be joint drug originators, with equal entitlement to claim paternity over the drug, in much the same way that copyright regimes offer moral (paternity) rights to authors (Rajan, 2002; Rigamonti, 2007; 2006).¹⁸⁰ While applying what is predominantly a copyright law concept to pharmaceutical innovation, one will no doubt require some adaptation. Illustratively, one could simply articulate the specific moral obligation, requiring a drug manufacturer to identify the IND/CTA applicant as a joint drug originator, in any labelling/packaging accompanying the drug. Alternatively, as with the current patent system in many countries that require the “inventor” to be identified in all patent applications, an INDA/CTA register could be maintained listing out all INDA/CTA applicants and the corresponding drug that is marketed.

The existence of a contingent right in favour of the IND/CTA filer also means that any firm that wishes to take the drug through trials can only do so after entering into a prior agreement with the IND/CTA applicant and such agreement may provide for payments to the IND/CTA filer.¹⁸¹

In order for such a contingent pre-clinical trial right to operate in favour of the IND/CTA applicant, it is important that the law vest the IND/CTA applicant with the exclusive right to test the said molecule through human trials for a certain period of time. Within this period, it must either commence the trials itself or elect to have its INDA approval acted upon, and the molecule taken through clinical testing by any other interested party. The regulator ought not to entertain any IND/CTA application covering the same drug from any other firm during this period of protection.

In other words, the regulator cannot entertain other IND/CTA applications for the same drug until such time as the trials are completed by either the IND applicant or an interested party as above-mentioned. If the drug is finally approved, the restriction on the ability of a third party to manufacture a follow-on drug continues, in view of the investment protection regime advocated in this article.

A conditional IND/CTA right operates as an additional incentive to small biotechnology firms, universities, public funded research institutions and other entities who might have sufficient resources and expertise to file an IND/CTA application, but not enough to take a molecule through human trials.¹⁸² The incentives include not only the prospect of recovery of costs, but also that of a joint right of paternity to be identified as a drug originator along with the firm that finally procures drug regulatory approval. It bears noting that any potential recovery of costs by the IND/CTA applicant from the final drug developer depends largely on the contractual terms between them. Further, the drug regulator ought not to disclose the molecule/substance comprising the prospective drug in question, but merely that it allegedly helps with a certain disease and the relevant contact information of the IND/CTA applicant. In other words, the disclosure ought to be only so much as to entice prospective drug developers in directly approaching the IND/CTA applicant and negotiating a contract with them; which would presumably include obligations to keep information revealed by the IND/CTA applicant confidential.

An added advantage of this model is that by conferring a limited first right to conduct trials based on the IND/CTA filing, wasteful expenditures generated out of competitive races are avoided, where multiple firms work on the same drug molecule and file similar submissions before the drug regulatory authority (Roin, 2009).¹⁸³

Trade Secrecy

An upstream third party invention could be protected as a trade secret (Gibbons and Vogel, 2007, p. 264),¹⁸⁴ whereby the inventor discloses it to others only under a contract of confidentiality, which stipulates the terms of disclosure.¹⁸⁵ It is possible that, apart from standard royalty terms, the agreement also stipulates that the final drug originator take into account the costs of the upstream inventor, while submitting its costs for the purpose of claiming reimbursement under the investment protection regime, as prescribed in this article.

The key advantage of a trade secrecy regime is that protection is automatic unlike patents, which entail an expensive formal registration process. Secondly, unlike patents, trade secrets are potentially of infinite duration and they last until such time that the secrets are independently discovered by a third party. Such independent discovery might occur in two ways. The first is the classic case of reverse engineering, where a product embodying the trade secret is placed in the market and the said product is “pried open” to discover the underlying idea. The second is where the same idea occurs independently to a third party.

The prospect of reverse engineering playing out in the drug discovery context is rather remote, given that the upstream discoverer is not likely to have any product embodying the idea.¹⁸⁶ Rather, in most cases, the discovery would have to be tested and developed into a marketable product (approved

drug) through an expensive and time-consuming process that lasts several years from the time when the upstream inventor first came up with the discovery.

Secret upstream inventions could be independently discovered by a third party. However, the scope for such independent discovery depends in part on how “inventive” or “non-obvious” the idea is. If the idea is relatively more obvious, it has a higher chance of being independently discovered. And if less obvious, it is likely to escape independent discovery for a longer period of time. However, if less obvious, the idea also has a greater prospect of being registered as a patent. In such a case, the upstream inventor will have to choose between patent protection and trade secrecy protection.

Publications, Reputational Gains and Collaborative Innovation

Apart from the prospect of being protected through trade secrecy and a limited IND right, upstream incentives may also exist in the form of reputational gains (Maurer, 2005a, p. 23) and publication prospects, particularly for those working in academic and research institutions. It is likely that such research institutions are recipients of public funding that permit their researchers to continue discovering new ideas without the need for any other external monetary incentive.

The Open Source Drug Discovery (hereinafter “OSDD”) project by the Indian Council for Scientific and Industrial Research (hereinafter “CSIR”) is an attempt to leverage non-patent incentives at the upstream level by *inter alia* fostering collaborative and open innovation between different researchers across the world who come together in their quest to find a cure for “TB” (OSDD, 2011).¹⁸⁷ Specific credits are offered to those participants who make valuable suggestions, and this serves as a good reputational non-patent incentive.

The above discussion points to the existence of a number of potential incentives to foster upstream invention by third parties. Given that there are significant non-patent incentives that could be availed of to ensure that upstream pharmaceutical research (by third parties) continues without serious disincentive, patent standards for upstream inventions could be kept at fairly high thresholds. This point is an important one to appreciate, given the proliferation of “me-too” drugs¹⁸⁸ involving the deliberate gaming of the patent system to extend monopolies by effectuating inconsequential changes to existing molecules.

Further, given that patents over upstream inventions have the potential of blocking down downstream drug development (Heller and Eisenberg, 1998, pp. 698–701), countries could also institute wide experimental use exceptions (Basheer and Reddy, 2010)¹⁸⁹ and compulsory licencing provisions.

Conclusion

While critics have arraigned the patent system for being predicated on an unproven innovation incentive foundation, they readily concede that pharmaceutical drugs are an exception. The logic underlying this concession is that patents are necessary to support the significant investments required to introduce a drug into the market. This article demonstrates that if the key concern is one of investment protection, the patent regime is sub-optimal, in that it only protects certain kinds of investments, that is, investments on inventions that qualify as “new” and “inventive”. Further, patents offer a uniform period of protection to all inventions, without regard to the actual investment per drug or its consequent social value.

Rather than attempting to shoehorn an investment protection function into the existing patent regime, I argue that one must evolve a distinct investment protection regime. The formulation of such a regime relieves the patent regime from the task of investment protection, a task for which it is ill-suited. Consequently, countries need not unduly lower their patentability thresholds in order to protect pharmaceutical investments.

While the “data exclusivity” regime aims to protect investments in drug development, it suffers from certain shortcomings such as a uniform period of protection for all drugs and a failure to consider the extensive costs associated with the drug discovery phase. I recommend an investment protection regime that is both comprehensive (in that it protects all costs associated with drug discovery and development) and proportionate (in that drug originators are compensated only to the extent of the costs associated with the specific drug under consideration). I also recommend that drug originators be offered a rate of return on investment that is proportionate to the health impact of the particular drug. In this way, the proposed investment protection regime helps shift the focus of R&D efforts from “me-too” versions to truly inventive drugs with significant social value.

Further, by permitting drug originators to include the costs incurred in relation to failed leads per target or even failed targets per disease, the regime incentivizes greater risk-taking, an aspect that is particularly important, given the increasing uncertainty associated with drug development today. The proposed regime delinks investment protection from “data reliance” and treats the issue as one of market exclusivity aimed at preventing free riders. An incidental advantage of the regime is that, over a period of time, one is likely to get a more accurate estimate of the average costs for drug discovery and development.

Given the problems associated with market exclusivities and their potential to engender excessive pricing, this article recommends the institution of compulsory licencing norms to foster more competition in the market and, thereby, lower prices. As an alternative, I propose a more broad based compensatory liability model based on cost sharing, where any follow-on entrant is free to manufacture the drug, upon the payment of reasonable compensation. I offer a novel framework for calculating such reasonable compensation that is arguably more optimal than existing models. This model is likely to be more effective and advantageous in those countries that already have drug-manufacturing capabilities and who wish to keep drug prices low. I also consider a model whereby the government reimburses the investments through tax credits and the like.

Although I demonstrate the sub-optimality of the patent regime, I note that the patent regime cannot be dispensed with owing to TRIPS, an internationally binding legal instrument. However, TRIPS is flexible enough to offer sufficient latitude to member states to keep their patent threshold high.

I end by noting some of the limitations of the proposed investment protection regime. Firstly, the proposed investment protection regime may not work well for all areas of innovation. Given that the creation of new drugs is closely associated with a structured and determinable regulatory process, it is relatively simpler to measure the value of output and compute investments that require to be protected within the pharmaceutical context. However, it may not be easy to apply a similar model to other areas of technology that do not possess a similar regulatory regime to filter output.

Secondly, given that we do not live in a perfect world, the investment protection regimes advocated in this article are not perfect models, if ever there was one. Rather, they are likely to entail implementation issues and operational costs, particularly in relation to the computation of costs. However, it can be expected that some of these issues will be amenable to resolution, as the model works through a number of years.

Thirdly, the proposed regime may not adequately incentivize the creation of drugs for “developing country” diseases or neglected diseases. Notwithstanding these problems, I argue that the newly proposed regime is one that is far more optimal than the existing patent regime, at least in so far as investment protection is concerned. Given that the patent regime seeks to foster innovation and creativity, it will be rather paradoxical if the regime itself were shielded from any innovative experimentation.

About the Author

Shamnad Basheer, MHRD Chaired Professor of IP Law, WB NUJS, Salt Lake III, Kolkata 700098, India; e-mail: shamnad@gmail.com.

Notes

This article is based significantly on the author's DPhil thesis submitted to the University of Oxford. He wishes to thank all those mentioned in the acknowledgement section of the thesis.

- 1 According to Landes and Posner, "the strongest case for patents in something like their present form is said to be found in a subset of the drug industry".
- 2 The novelty and non-obviousness principles are designed to work together to ensure that the patent monopoly is available only for genuinely new inventions. The novelty standard asks whether the invention has been previously described or practiced, and actually looks at previous references and practices; it thus determines whether the invention is within the existing state of the art. The non-obviousness principle then asks whether the invention is an adequate distance beyond or above that state of the art; it clearly and unavoidably, therefore, involves a judgement call.
- 3 The term compensatory liability appears to have been coined first by Professor Reichman. See Reichman (2000).
- 4 See section entitled "The Risk of Diluting Patentability Criteria".
- 5 See section entitled "Measuring Health Impact".
- 6 Compare Huskamp who notes "[t]he first brand drug using a particular therapeutic mechanism of action is called a 'breakthrough drug,' while brand drugs that use the same mechanism of action but enter after the breakthrough drug are called 'me-too drugs' "(Huskamp, 2006). With US Congress Office of Technology Assessment, which, in a report, notes that however, the distinction between pioneers and me-too's is described as "fuzzy", since not all me-too drugs may be imitative (US Congress of Technology Assessment, 1993).
- 7 "Evergreening" is not a formal concept of patent law. It is best understood as a social idea used to refer to the myriad ways in which pharmaceutical patent owners utilize the law and related regulatory processes to extend their high rent-earning intellectual monopoly privileges, particularly over highly profitable (either in total sales volume or price per unit) "blockbuster" drugs. For a discussion on this point, see Faunce and Lexchin (2007); see also *infra* notes 156–158 and accompanying text.
- 8 See Federal Food, Drug and Cosmetic Act, which defines a "drug" as an "article intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man or other animals".
- 9 Rader, after noting the multifarious definitions of the term "bio-pharmaceutical" offers the following definition: "a pharmaceutical product manufactured by biotechnology methods (involving live organisms)".
- 10 Although biologics "are large protein molecules derived from living cells and manufactured through DNA or RNA synthesis", conventional drugs "are small molecules derived from chemical synthesis", and additionally, conventional drugs "typically have well-defined structures".
- 11 Defining *in vitro* to mean something done or produced in a laboratory using a glass plate or test tube.
- 12 The CTA application includes a group of scientific documents called an Investigational Medicinal Products Dossier (hereinafter "IMPD").
- 13 The first such study by the Tufts Center, in 1979 proclaimed that the true cost to develop a new drug was USD 54 million. In 1991, the Tufts Center updated the study and pegged the cost at USD 231 million. Finally, the figure for the year 2000 was USD 802 million.
- 14 Light states that "The Public Citizen team used a simple, back-of-the-envelope method for calculating R&D expenses, but this method is intuitively appealing".

- 15 Light notes that “[T]he sample was non-random and small, using only ten firms. Originally, the researchers invited twenty-four firms, using unstated criteria, and twelve of them declined for unstated reasons. The other twelve corporations chose to participate, but two provided inadequate data”.
- 16 See DiMasi *et al.* (2008).
- 17 Light notes that “If one-third of new drugs average USD 800 million in R&D costs and two-thirds average one-quarter of that cost, or USD 200 million, then should not the CBO point out that the overall average is only USD 400 million?”
- 18 The problem of free riding and the issue around appropriability that it generates is a recurring theme in the literature around patents and innovation. Illustratively, see Mark A. Lemley (2005, pp. 1031, 1035).
- 19 Burk and Lemley note: “Patent law is our primary policy tool to promote innovation, encourage the development of new technologies, and increase the fund of human knowledge. To accomplish this end, the patent statute creates a general set of legal rules that govern a wide variety of technologies”.
- 20 Hall notes: “The principle behind the modern patent is that an inventor is allowed a limited amount of time to exclude others from supplying or using an invention in order to encourage inventive activity by preventing immediate imitation”.
- 21 See also the US Constitution article 1, §8, cl. 2 (acknowledging explicitly the incentive theory by providing that Congress has the power “to promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries”).
- 22 Notable examples of inventions that came about without the incentive of a patent include Zacharias Janssen, who invented the first compound microscope in 1595 and Johannes Gutenberg who is credited with inventing the first printing press. Boldrin and Levine state that a number of historically important developments in the field of agriculture, electronics and cryptography took place without any patent protection.
- 23 Torrance and Tomlinson state that “despite the economic logic of the conventional view, there exists surprisingly little empirical evidence to support the key assumption that patents do actually spur technological innovation”.
- 24 Mark A. Lemley, discussing the rational ignorance at the patent office, argues:

The patent system intentionally restricts competition in certain technologies to encourage innovation. Doing so imposes a social cost, though the judgment of the patent system is that this cost is outweighed by the benefit to innovation . . . There is a great deal of literature attempting to assess whether that judgment is accurate or not, usually without success.

- 25 But see Howells, who claims that the treatment of these specific historical examples of blocking and the analysis by Merges and Nelson on this count is not sound (Howells, 2008, p. 164).
- 26 Scherer notes that the traditional economic justification for patents has likely always encompassed the promotion of development and commercialization efforts in addition to inventive activity.
- 27 Sichelman cites examples of inventions that never translated to commercially viable productions such as the “anti-eating face mask” (disclosing a medieval-looking mask that prevents the wearer from eating), “beer bottle mini-umbrella” (disclosing a “beerbrella”, a small umbrella that attaches to a beer bottle to keep the bottle shaded) and “weed-cutting golf club” (disclosing a weed-whacker in the shape of a golf club).
- 28 See US patent no. 5425497 (filed June 20, 1995; relating to Jay Sorensens’s coffee cup sleeve, a simple invention that would have incurred minimal costs of development).
- 29 Mazzoleni and Nelson (1998) assert that patents are unnecessary they note that, “[I]n a wide range of circumstances . . . [t]he advantages conferred by a head start . . . seem to provide ample incentive for the follow-on work”.

- 30 Scherer note that “[e]ven without patents, the firm that would seek to imitate the Boeing 787 would [end up] . . . spending very nearly as much as Boeing did to develop its 787”.
- 31 Some scholars propose the institution of a separate commercialization patent in order to incentivize the development of inventions. See Sichelman (2010).
- 32 Kingston concludes that patents fail to adequately promote innovation in most fields other than chemicals and pharmaceuticals, where the “invention-innovation link is . . . strong”.
- 33 See *Sanofi-Synthelabo v Apotex Inc.*, 470 F.3d 1368, 1383 (Fed. Cir. 2006), appeal docketed, no. 2007–1438 (Fed. Cir. September 4, 2007); see also *Pfizer Canada Inc. v Apotex Inc.*, 2009 FCA 8, [2009] 4 F.C.R. 223 (noting that “[t]he patent system is intended to provide an economic encouragement for research and development. It is well known that this is particularly important in the field of pharmaceuticals and biotechnology”).
- 34 Merges and Nelson note rightly that, “increases in research and development expenditures yield more inventions”.
- 35 Almost all patent regimes premise the grant of a patent on a demonstration that the claimed invention is new and non-obvious to a person skilled in the art. This requirement has been articulated in article 27.1 of the TRIPS as well, which mandates that every invention which is new, inventive and useful shall be granted a patent. See Agreement on Trade-Related Aspects of Intellectual Property Rights article 27.1, April 15, 1994, Marrakesh Agreement Establishing the World Trade Organization, annexure 1C, Legal Instruments—Results of the Uruguay Round, 1869 U.N.T.S. 299, 33 I.L.M. 1195 (1994; hereinafter TRIPS).
- 36 See *Bonito Boats, Inc. v Thunder Craft Boats, Inc.* 489 US 141 (1989; holding that the novelty and non-obviousness requirements “are grounded in the notion that concepts within the public grasp, or those so obvious that they readily could be, are the tools of creation available to all”).
- 37 Reichman (2009) notes that

[t]o avoid these conceptual errors, I have long urged policy makers to sharpen the distinction between exclusive rights that aim to stimulate technological progress and alternative measures that aim to protect investments as such. This distinction is particularly important in cases where second comers may too easily capture the fruits of investment by avoiding or circumventing the cost structure that legitimate competitors must otherwise defray (Reichman, 2009, p. 43).

See also Reichman (2000).

- 38 See US patent no. 5425497 relating to Jay Sorensens’ coffee cup sleeve, a simple invention that would have incurred minimal costs of development); see also Barton (2003, pp. 475–508) describing a series of similar patents that have issued on insulating sleeves for paper; he takes issue with such patents on grounds of economic theory, arguing that since such inventions were cheap to discover and develop, they would have emerged even without the prospect of patents; see also Dreyfuss (2000), who makes a similar argument in the context of business method patents:

. . . sticky business methods are their own reward. With lock in, network effects, and even good old fashioned loyalty, lead time (the first mover advantage) goes a long way to assuring returns adequate to recoup costs and earn substantial profit. In sum, while business innovations are certainly desirable, it is not clear that business method patents are needed to spur people to create them (Dreyfuss, 2000, p. 275).

Therefore, such methods do not necessarily require any patent incentives to drive their creation, as the costs of creation and implementation are low.

- 39 Roin notes, “[u]nder the novelty requirement, negligible disclosures can prevent—and have prevented—socially valuable drugs from being patented”.

- 40 The PDE VA inhibitor is a specific kind of phosphodiesterase inhibitor with a highly pronounced relaxant response. The use of Sildenafil Citrate as a PDE VA inhibitor was found to induce a pronounced and significant erectogenic effect in patients with an erectile dysfunction.
- 41 *Lilly Icos Llc v Pfizer Ltd.* (1) (2002) EWCA Civ. 1, available at <http://www.bailii.org/ew/cases/EWCA/Civ/2002/1.html> [Accessed January 2011] (citing the article in the Times entitled, *Viagra earns Dome place as Best of British*, published on April 20, 1999 which stated that “Viagra has won a place as one of the brightest British innovations of the 1990s”).
- 42 Sildenafil Citrate essentially works by inhibiting an enzyme that retards the relaxation of the penile muscle. The relaxation of penile smooth muscle is traceable to chemicals called cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). cGMP and cAMP are rendered ineffective by the action of a PDE enzyme. Viagra helps restore the potency of cGMP and cAMP by inhibiting the PDE enzyme with the help of certain other chemicals called PDE inhibitors.
- 43 See *Lilly Icos Llc v Pfizer Ltd.*, where the Court of Appeal in the United Kingdom upheld the High Court decision delivered by Laddie, J., in this regard (*Pfizer Ltd. v Lilly Icos Llc.* [2000] EWHC Patents 49).
- 44 Two earlier Pfizer patent applications, namely EP 0463 756 and EP 0526 004, referred to, respectively, as Bell I and Bell II, covered Sildenafil Citrate, along with a number of other chemicals, and claimed their use for a number of medical applications, but not the treatment of MED specifically. However, these patents disclosed the use of Sildenafil Citrate as a PDE inhibitor for the treatment of complaints as angina and hypertension.
- 45 See *Lilly Icos Llc v Pfizer Ltd.*, at para. 54 last visited (citing the key prior art evidence as Rajfer J. *et al.*, 1992).
- 46 TRIPS, article 33 reads as “The term of protection available shall not end before the expiration of a period of twenty years counted from the filing date”.
- 47 In patent law, lack of determinacy has the potential to undermine a fundamental goal of the patent system—providing an incentive for creators to invent and to publicly disclose their inventions . . . With an exceedingly uncertain reward, the incentive effect may diminish (Mullally, 2010, p. 1109). See also Petherbridge (2010), defines the term “legal determinateness” as “capacity of the rules of the law when confronted with a claim to a new invention to conclusively settle patentability—without the need to resort to a costly inquiry into easily disputable factual conclusions”.
- 48 Lane notes that obviousness is the most unsettled condition of patent validity, when viewed in terms of quantity of litigation.
- 49 Brill notes that the inherent uncertainty accompanying patent law, especially with regard to such matters as the application of the doctrine of equivalents, meeting of burdens of proof, “battles of experts”, inequitable conduct and more.
- 50 “The non-obviousness principle . . . asks whether the invention is an adequate distance beyond or above that state of the art; it clearly and unavoidably, therefore, involves a judgment call” (Barton, 2003); see also Petherbridge (2010, p. 907) noting that while the concept of obviousness is simple enough to state, it has proven tremendously difficult to operationalize, “the basic policy of obviousness is that advances not apparent to an ordinarily skilled artisan are those that advance human understanding sufficiently to justify the grant of a patent . . . [t]he measurement cost of obviousness is tremendous”.
- 51 Darrow discusses different aspects of enantiomers.
- 52 See *Generics (UK) Limited and others v H Lundbeck A/S* (2009) UKHL 12.
- 53 See *Lundbeck A/S v Neolab Ltd. et al.* (Escitalopram), invalidity proceedings, Federal Supreme Court, Germany, September 10, 2009, docket number Xa ZR 130/07.
- 54 See *Apotex v Lundbeck Canada Inc.*, 2010 FCA 32.
- 55 See *H. Lundbeck A/S v Alphapharm Pty. Ltd.* (2009) FCAFC 70.

- 56 See *Alfred E. Tiefenbacher GmbH v H. Lundbeck A/S*, 312468 / HA ZA 08–1827 (District Court); see also Phillips (2009)
- 57 See *Lilly Icos Llc v Pfizer Ltd.*
- 58 Compare *Pfizer Canada Inc. v Apotex Inc.* (F.C.A.), 2009 FCA 8 (2009) 4 F.C.R. 223, paras 28–31 (following the standard laid down by the Canadian Supreme Court in an earlier pharmaceutical case, *Apotex Inc. v Sanofi-Synthelabo Canada et al.* 2008 SCC 61), with *Apotex Inc. v Sanofi-Synthelabo Canada et al.*, 2008 SCC 61 (holding that “For a finding that an invention was ‘obvious to try’, there must be evidence to convince a judge on a balance of probabilities that it was more or less self-evident to try to obtain the invention. Mere possibility that something might turn up is not enough”).
- 59 The United States and other leading patent jurisdictions hold non-obviousness or inventive step to be a question of law, predicated on underlying facts; see, for example, *In re Kubin*, 561 F.3d 1351, 1355 (Fed. Cir. 2009);, “Obviousness is a question of law based on underlying findings of fact”); see also Cotropia (2007) noting that “[o]wing to the highly intensive fact specific nature of the enquiry and the subjectivity of the assessment, it is evident that courts may come to differing conclusions on the facts of the same case”.
- 60 See *Pfizer Canada Inc. v Apotex Inc.*, at para. 107 where the court noted “[t]he test applied by Mr. Justice Laddie appears to be met if the prior art indicates that something may work, and the motivation is such as to make this avenue ‘worthwhile’ to pursue. This approach which is based on the possibility that something might work, was expressly rejected by the Supreme Court in *Sanofi-Synthelabo*”.
- 61 Commentators however argue that recent data reveals that the number of victories by patent owners at UK courts has been steadily increasing. See Moss *et al.* (2010, pp. 148–57).
- 62 *Harries v Air King Products*, 183 F.2d 158, 162 (2d. Cir. 1950; per Judge Learned Hand; characterizing the non-obviousness requirement as being “as fugitive, impalpable, wayward and vague a phantom as exists in the whole paraphernalia of legal concepts”).
- 63 The evaluative nature of the inquiry also implies that reasonable people, including judges, juries, patent examiners, or even the rather mystical imaginary persons skilled in the art, can easily reach different conclusions at different times, thus making it extremely difficult to foretell the result of an obviousness attack or objection. This unpredictability has led to the arbitrary use of discretion and to accusations of uncertainty (Minssen, 2010, p. 63).
- 64 William Cornish, *The Essential Criteria for Patentability*, 14 IIC 765, 771 (1983). See also Machlup (1958), who argues: “The patent system lacks logic . . . Its critics have described the patent right as “a lottery in which it is hardly worthwhile taking out a ticket”.
- 65 Abramowicz and Duffy argue that the inventive step test has largely been interpreted through a cognitive lens, focusing on whether individuals have epistemic awareness of technological solutions to problems.
- 66 Furrow notes:

The recent decision by the *Supreme Court in KSR International v Teleflex Inc.* poses a threat to the present balance, and pharmaceutical innovators in particular are at risk of losing some of the essential patent protections that allow them to recoup their drug discovery and development investment (Furrow, 2008, p. 276).

- 67 *Pfizer Inc. v Apotex*, 488 F.3d 1377; 2007 US App. LEXIS 11886; 82 U.S.P.Q.2D (BNA) 1852 (Rader, J.); see also *Teva Pharmaceutical Industries Ltd. and others v Istituto Gentili SpA and Merck & Co. Inc.*, (2003) EWHC 5 (Pat), where Jacob, J., invalidated two of Merck’s UK alendronate “use” patents with some remorse and noted:

I accordingly hold both patents invalid. I do so with some regret. Merck have only had a few years’ exclusive exploitation of alendronate. They must surely have had to make a very considerable investment and incurred considerable risk in bringing it to market. And mankind

is better off as a result. But the patent system does not confer monopolies on those who develop obvious or old products, even if they have never been exploited. A workable system for that might be a good idea, particularly in the field of medicines and analogous fields.

- 68 Some judicial decisions have alluded to the proposition that expensive experimentation tends to infuse a hue of “inventiveness” to the alleged invention. See, for example, *Edoco Technical Products, Inc. v Peter Kiewit Sons’ Co.* 313 F. Supp. 1081 (1970; the district court upheld the inventiveness of the invention on the ground that “a long and expensive period of experimentation was required by the patentees to solve the problem . . .”).
- 69 A traditional patent system is “designed to spur the creation of new and non-obvious knowledge” (Sichelman, 2010, p. 345).
- 70 Rich states that non-obviousness is “the ultimate condition of patentability”; see also Duffy and Merges (2007, p. 612) categorizing the non-obvious requirement as the “final gatekeeper”.
- 71 These include the United States, European Union and Japan. The list is constantly increasing due to provisions in various Free Trade Agreements (FTAs) that mandate data exclusivity. See, for example, Fink and Reichenmiller (2006, pp. 285–300).
- 72 See generally Mossinghoff (1999); see also Eisenberg and Heller (1998).
- 73 Ultimately, it is important to bear in mind that every potential inventor is also a potential infringer. Thus, a “strengthening” of property rights will not always increase incentives to invent; it may do so for some pioneers, but it will also greatly increase an improver’s chances of becoming enmeshed in litigation. Indeed this is the very heart of our case (Merges and Nelson, 1990, p. 916).
- 74 Banik and Kesan note that “[p]atents also impose social costs such as reduced levels of competition or wasteful design-around efforts by competitors. Thus, efficient patent systems aim to induce investment in R&D while limiting losses due to market power”.
- 75 IFPMA notes that United States, EU, Australia, New Zealand and Israel currently provide for data exclusivity.
- 76 See 21 U.S.C. §355(a).
- 77 See 21 U.S.C. §355(b).
- 78 See 21 U.S.C. §355(j).
- 79 Drugs based on new chemical entities, are entitled to an exclusivity period of 5 years. See 21 U.S.C. S. 355(j)(5)(F)(ii). See also Dickinson (1999).
- 80 This exclusivity of 7 years is granted only to approved “orphan” drugs, defined under the Orphan Drug Act 1983 as those products that treat rare diseases and conditions affecting less than 200,000 patients in the country. The act is designed to combat the general unwillingness of pharmaceutical manufacturers to invest in the development of commercial drugs for the treatment of diseases, which, although devastating to their victims, afflict too small a proportion of the population to make them commercially viable. See Orphan Drug Act, Pub. L.97–414, §1(b)(4)-(5), 96 Stat. 2049, 2049 (1983) (Congress’ findings); H. R. Rep. No. 840, 97th Cong., 1st Sess. 1, reprinted in 1982 US Code Cong. and Admin. News 3577, 3577.
- 81 This exclusivity of 6 months is granted to encourage studies to determine whether existing drugs are safe and effective for paediatric populations. See The Food and Drug Administration Modernization Act 1997, S.111, P.L. 105–115. Paediatric exclusivity is unique in that it is not a stand-alone exclusivity protection, but attaches itself as an additional period to already existing periods of exclusivity that the drug is entitled to.
- 82 This category includes any application for an existing drug (containing a previously approved active ingredient), for which a new use or indication has been discovered. Upon the generation of clinical trial data pointing to such new uses, new dosages or new indications, the said drug is entitled to 3 years of data exclusivity.

- 83 European Commission, Directive 2004/27/EC, article 10.1.
- 84 European Commission, Directive 2004/27/EC, art. 10.1.
- 85 The Patient Protection and Affordable Care Act contains within its fold a sub-section titled the “Biologics Price Competition and Innovation Act” (BPCI). The BPCI in turn amends the Public Health Services Act to provide for abbreviated pathway for biologics. See 42 U.S.C. 262(k)(2)(A)(i)(I).
- 86 The Patient Protection and Affordable Care Act.
- 87 42 U.S.C. 262(k)(7)(A).
- 88 See European Commission, Directive 2004/27/EC, article 10.4.
- 89 Merrill notes that “[t]here is a general agreement that the Orphan Drug Act produced the economic incentives needed to promote drug development of drugs for rare diseases”.
- 90 “Patent eligibility” broadly refers to the requirement that a subject matter for which a patent is sought be inherently suitable for patent protection, in the sense of falling within the scope of subject matter that patent law prima facie exists to protect. The term ‘patentability’, on the other hand, refers to those set of principles that inform the requirements that must be satisfied for a patent eligible subject matter (i.e. an invention) to be granted a valid patent. Principally they are the requirements of novelty, inventiveness (non-obviousness), utility (industrial applicability) and sufficient description. (Pila, 2003, pp. 341–2)
- 91 See discussion in section entitled “The Relative Indeterminacy of Patent Standards”.
- 92 Sichelman notes that the patent “reward” theory “is premised on providing incentives for nascent inventions, not commercialised end products”.
- 93 See also discussion in section titled “The Relative Indeterminacy of Patent Standards”.
- 94 Eisenberg notes that FDA granted statutory exclusivities “would significantly reduce costs involved in litigation, are less prone to abuse and would create legal certainty that is currently missing from the protection of technological innovation under patent law”. See also Roin (2009, p. 507); Eller (2010).
- 95 In 2007, the National Academies Committee on Science, Engineering and Public Policy called for the United States to adopt the European data exclusivity period of 10–11 years.
- 96 Roin believes that the current period of data exclusivity offered in the United States is not sufficient and recommends that it be extended to anywhere between 10 and 14 years in order to “provide a rough substitute for patent protection”. See Roin (2009).
- 97 It must be noted that these costs have been revised significantly and the latest estimates suggest USD 1.3 billion. However, the USD 802 and USD 335 million figures broadly indicate the proportion of costs between drug discovery and development. See DiMasi *et al.* (2003, p. 165).
- 98 See *supra* text accompanying notes 14–17.
- 99 Compare DiMasi *et al.* (2003, pp. 152–3) stating the estimates made that included the cost of failures, with News in Avance (Avance, 2007) criticizing and questioning the inclusion of failures in these figures.
- 100 Stating that “Glivec” was marketed as “Gleevec” in the United States for the use of chronic myeloid leukaemia.
- 101 See US patent no. 5521184 (April 1993).
- 102 See US patent no. 6894051 (January 2000) (The patent was first filed in Switzerland in July 1997 and then subsequently in the United States in 2000, claiming priority from the Swiss filing.)
- 103 Li *et al.* note that experience from the bio-pharmaceutical industry indicates that currently only 5% of newly explored targets eventually lead to FDA-approved products.
- 104 Although this cost inclusion net is fairly wide, it excludes investments pertaining to wrong targets. Expanding the cost cover to include such failed targets could blur the lines of what counts as a legitimate cost to compensate (as it makes it more amenable to cost exaggeration and uncertainty). Given that public funding is widely prevalent in such areas of basic research, it is hoped that such exclusion would not have a significantly deleterious impact on the rate of investment.
- 105 This is to prevent any double counting of costs.

- 106 See *infra* text accompanying note 159.
- 107 Estimates vary, but the pharmaceutical and medical device industries spend around \$30 billion per year on marketing efforts designed to maximize market share, and doctors are one of their main targets. On average, the drug and medical device industries spend over \$20,000 per doctor each year on marketing efforts that include gifts, meals, travel, consultancy fees and continuing medical education programs. The reach of medical marketing has grown so broad that one recent survey reported that 94% of physicians have received some form of benefit or payment from the drug and device industries (Weiss, 2010, pp. 260–1).
- 108 PhRMA argues that pharmaceutical marketing and promotion helps provide information to doctors about new medicines: “Pharmaceutical marketing plays a valuable role by delivering the newest information on medicines to physicians and helping to translate new technologies into practice”(PhRMA, 2008, p. 5). Also, direct-to-consumer advertising raises consumer awareness about diseases and new treatment options (PhRMA, 2008, p. 12).
- 109 There are a number of key reasons for concern about the impact of pharmaceutical companies’ marketing strategies. These include
- The fact that drug promotion is often misleading.
 - The risk of disease mongering.
 - The increasing costs of drugs within national health systems.
 - New drugs are the ones most heavily promoted and these are the ones with the least well-understood safety profiles (Buckley, 2004, p. 7).
- 110 As per Gagnon and Lexchin’s estimates, pharmaceutical companies today spend twice as much on promotion as they do on drug R&D.
- 111 Bell *et al.* argue that the “public health community needs to create mechanisms for providing consumers with objective, independent information about available drug therapies, including their indications, risks, benefits and alternatives. Such information must be placed in the context of education about medical conditions”. The excessive reliance on marketing-driven and industry-provided promotional information on medicinal drugs may be successfully abated if countries provide the legal framework for the creation of alternate efficacious information dissemination systems, which will enable patients and healthcare professionals to undertake their own individual assessment of newly introduced drugs based on adequate knowledge of their safety in the local community, their therapeutic benefits or their cost-effectiveness compared with the older drugs they replace. See Institute of Community Medicine (2012).
- 112 For an illustration of scholars who have used the CAPM and F–F models, respectively, over the years to calculate pharmaceutical CoC, see Harrington (2012, p. 79).
- 113 Calculating the opportunity CoC may be a common financial practice, but our aim was to stress to journalists and policy makers that 51% of the total DiMasi/PhRMA R&D estimate was a theoretical expense—opportunity cost—not a real one. Drug companies do not “pay” for opportunity cost in the literal sense (Public Citizen, 2010).
- 114 See generally Orphan Drugs Act 1983 (Unlike other types of exclusivities for new drugs, as regards orphan drugs, the law provides complete market exclusivity for a 7-year period, thereby, preventing a competitor from entering the market, even if it were able to generate its own data.)
- 115 See also *Genentech, Inc. v Bowen*, 676 F. Supp. 301, 307 (D.D.C. 1987).
- 116 See Orphan Drug Regulations, 57 Fed. Reg. 62,076, 62,081 (1992) at 62,078.
- 117 See Orphan Drug Regulations, 57 Fed. Reg. 62,086 (1992).
- 118 The terms therapeutic advantage and clinical superiority are interchangeable. Therapeutic advantage is demonstrated when clinical testing of a drug demonstrates it to be superior in an important dimension. 21 C.F.R. §316.3 (b) (3) (iii) (1999).
- 119 Basheer and Amin note that Roche was the exclusive licensee of Gilead, which owned the patent covering “Oseltamivir”.

- 120 However, the prices would depend to some extent, on the amount of royalties that are required to be paid to the drug originator.
- 121 See the Indian Patents Act 1970, §84; see also *Natco Pharma Ltd. v Bayer Corporation*, C.L.A. no. 1 of 2011 (marking India's first compulsory licencing decision in the post-TRIPS era, this order granted a license to an Indian generic company, Natco to manufacture and sell a generic version of Bayer's kidney/liver cancer drug Nexavar. The decision was given on the basis that the drug was available to only 2% of the total number of eligible patients, the drug was not "reasonably affordable" to the public and also, pertinently that the drug was not manufactured "to a reasonable extent" in India, thereby meeting all of the three mutually exclusive criteria for grant of a compulsory license under section 84 of the Indian Patents Act 1970); see also Basheer (2012).
- 122 See Reichman (2000), who appears to have coined this term for the first time to refer to models of IP protection that eschewed exclusivity and provided only compensation to the IP owner.
- 123 See US Federal Insecticide, Fungicide and Rodenticide Act, 7 U.S.C. §136a3(c)(1)(F)(iii) (2000).
- 124 See 7 U.S.C. §136a3(c)(1)(F)(i) (2000).
- 125 See 7 U.S.C. §136a3(c)(1)(F)(i) (2000).
- 126 FIFRA §136a(c)(1)(D)(ii) (1982).
- 127 See *Stauffer Chemical Co. v PPG Industries*, docket no. 16-199-077-822, Federal Mediation and Conciliation Service (1983); see also Coll (1986).
- 128 Dinca notes that "[i]n this model, the single element that should be settled by the legislator is the duration of protection".
- 129 "Given that Canada used to impose a standard four percent royalty on a license of right to use patented pharmaceuticals until 1992, one could envision that figure as an outer limit . . ." (Reichman, 2009, p. 35).
- 130 The Commissioner of Patents has also never found arguments convincing enough to vary the amount of the royalty arbitrarily set at 4% of the net selling price of the drug in the first decision rendered under the provisions of 1969, in spite of numerous submissions made by patentees as to the amount of money they actually spent in R&D in Canada and/or abroad. .
- 131 See discussion in section entitled "The Fellmeth Model".
- 132 See *supra* text accompanying note 128.
- 133 Lemley and Weiser lament the fact that in all the debates about property versus liability rules, scholars often tend to ignore issues of institutional competence and costs.
- 134 Love proposes and presents an alternative to the patent system inter alia in the form of "direct funding of drug development" on the basis of his work in his earlier paper with Tim Hubbard; see also Baker (2005 who notes the inefficiencies plaguing the current system of patents and suggesting government funded research as an alternative to patents since it already occurs on a "massive scale"; see also The Free Market Drug Act, H.R. 5155, 108th Congress (2004; seeking to create a number of public research corporations which would not only conduct basic research but also all the development required to gain approval from the FDA, although this idea never translated into law).
- 135 Cost increases in clinical trials, especially during stage (III) trials, have made the overall production cost of a new chemical entity prohibitively expensive. One proposal to achieve these ends that appears very appealing is the idea to publicly fund clinical trials in pharmaceuticals (Jayadev and Stiglitz, 2010, p. 222-3).
See also Reichman (2009).
- 136 NIH spends more than USD 31.2 billion annually in medical research (May SW for the people of America/Americans) (last updated March 9, 2011) National Institutes of Health (2012). Dorsey *et al.* (2005) indicate that the United States appears to be the leading governmental contributor to global public health expenditure.

- 137 R&D tax credits can either be comprehensive or incremental. While a comprehensive tax credit applies to all R&D spending (e.g. Canadian tax credit model), an incremental tax credit system targets the increase in R&D spending from the base year R&D spending. See Russo (2004, p. 319); see also, Hall and Reenen (2000, p. 466) who report that incremental schemes with moving average greatly reduce the incentive effect of the credit.
- 138 Deloitte undertook a survey of R&D tax incentives in 25 countries.
- 139 Internal Revenue Code, 26 U.S.C. S45(C).
- 140 See CIRD75050, HM Revenue & Customs, <http://www.hmrc.gov.uk/manuals/cirdmanual/CIRD75050.htm> [Accessed April 2012]; CIRD76000, HM Revenue & Customs, <http://www.hmrc.gov.uk/manuals/cirdmanual/CIRD76000.htm> [Accessed April 2012].
- 141 Nick Bloom *et al.* (2002) note that “[o]ur primary conclusion is that fiscal provisions matter . . . tax changes significantly effect the level of R&D even after controlling for demand, country-specific fixed effects and world macro-economic shocks”). Czarnitzki *et al.* note that “we find that R&D tax credits have a positive impact on the firm’s decision to conduct R&D. They also increase innovation output of the recipient firms. Tax credit recipients realize a higher number of product innovations, as well as sales of new and improved products”.
- 142 Hall and Reenen speak about firms “shifting expenses around in their accounts to maximize the portion of R&D that is qualified” for the tax credit.
- 143 Hall and Reenen argue that the efficacy of tax credits often depends on the nature of the firm(s) entitled to the credit. Illustratively, new entrants or firms in recession may not be able to use the full value of certain credits, since they may not have sufficient taxable profits.
- 144 Napoleon was keen on finding an effective way to feed his troops in areas where food could not otherwise be procured locally. In 1809, Nicolas François Appert won the prize for his solution, which involved heating, boiling and then sealing the food to be preserved in airtight glass jars. The basic principles of canning have not changed much since Nicolas Appert’s methods were published.
- 145 Apart from an international treaty that obligates countries to pay moneys into a common fund, commensurate with their respective per capita income, funding could also flow from private philanthropic organizations (Hollis, 2008, p. 130).
- 146 Love justifies the “direct funding of drug development” alternative to patent on the ground that, “[i]f exclusive marketing rights were eliminated for pharmaceutical drugs, prices would be far lower, and governments could re-direct significant resources to these types (or different types) of non-profit drug or vaccine development entities”.
- 147 An Advanced Market Commitment (hereinafter “AMC”) or an Advanced Purchase Contract (hereinafter “APC”) is primarily aimed at providing sufficient “market” incentives to foster the creation of new drugs, particularly vaccines, for Type III neglected diseases that disproportionately afflict low income countries. See Berndt and Hurvitz (2005, p. 654). AMCs are commitments made by governments and non-profit organizations to offer a fixed price to a drug originator who comes up with a specified new drug. See Maurer (2005b, p. 3).
- 148 However, such relinquishing will only operate in relation to similar versions of the drug that are protected under the investment protection model. In other words, the drug originator should be free to sue on the basis of its patent right, when the said patent is used in conjunction with an unrelated drug (a drug that is not same or similar to the initial drug under consideration, for which the investment protection model operates).
- 149 See discussion on prizes in section entitled “Reimbursement Model”.
- 150 When the payment per QALY drops too low, firms are likely to opt out of the HIF and prefer patents instead. See Hollis (2008, p. 129) .

- 151 Panel Report, Indonesia- Certain Measures Affecting the Automobile Industry, WT/DS54/R (July 2, 1998; hereinafter Indonesia Autos Panel Report).
- 152 The United States also argued its national treatment obligations under article 3 of TRIPS, since the programme discriminated against nationals of other WTO member states in respect of acquisition and maintenance of trademarks.
- 153 Indonesia Autos Panel Report, at para. 14.271. The United States also argued that owing to its foregoing of the use of the global mark on cars manufactured for the Indonesian programme, the said global mark could be rendered susceptible to cancellation in Indonesia due to non-use. The panel however rejected this argument. See Indonesia Autos Panel Report at para. 14.270.
- 154 According to the NIH, given that drug discovery and development is conducted with the help of public funding in many cases, it would amount to over-compensation if such funding were not deducted from the overall costs claimed.
- 155 See Boldrin and Levine state that only 25–30% of the total R&D expenditure goes towards new drugs, with the rest being utilized for the development of me-too drugs; see also Huskamp (2006).
- 156 Evergreen trees are present in areas where there is either no unfavourable period for growth, or the growing season is very short. Arora (2004, p. 123) explains that the term “evergreen” is used for a woody perennial plant that is bearing and losing leaves continuously throughout the year. For more information, see Thomas (2000, pp. 28–9).
- 157 Thomas notes that evergreening is “a potentially pejorative (sic) term that generally refers to the strategy of obtaining multiple patents that cover different aspects of the same product, typically by obtaining patents on improved versions of existing products”.
- 158 See *Whirlpool Corp. v Camco Inc.*, (2000) 2 S.C.R. 1067, para. 37. (Defining evergreening in the context of “double patenting” by noting that, a patentee who can “evergreen” a single invention through successive patents by the expedient of obvious or uninventive additions prolongs its monopoly beyond what the public has agreed to pay.) For an interesting discussion see Machlup (1958) discussing that the phenomenon of evergreening dates back to at least the 1930s and citing to the 1939 TNEC Hearings, which discussed the patenting of minor improvements to continue protection of the original invention.
- 159 Swidey states that Esomeprazole is the S-enantiomer of omeprazole (marketed as Losec/Prilosec), and AstraZeneca claims improved efficacy of this single enantiomer product over the racemic mixture of omeprazole. However, this alleged efficacy has been severely disputed.
- 160 See *supra* note 81.
- 161 Merges (1993) notes that, “firms try to characterize as many expenses as possible as R&D-related for purposes of the R&D tax credit”, in the context of tax credits.
- 162 Creative accounting is defined as a “[f]orm of accounting which, while complying with all regulations and practices, nevertheless gives a biased impression (generally favourable) of an entity’s financial performance and position” (Chartered Institute of Management Accountants, 2005, pp. 64–5).
- 163 Koh Jun notes that “[t]here is also a risk for companies to maximize tax claims by means of creative accounting”.
- 164 See §25(1) and (2), Indian Patents Act 1970. (In India, e.g. a patent can be opposed by a third party on extensive grounds both before and after grant of the patent.)
- 165 The PhRMA report contains an overview of the price control regimes of various countries.
- 166 See *United Brands v Commission* (1978) 1 CMLR 429; *CICCE v Commission* (1985) ECR 1105. See also *The Supply of Banking Services by Clearing Banks to Small and Medium Sized Enterprises*, Competition Commission, 5319 (2002), a case concerning excessive pricing in the supply of banking services by clearing banks to small and medium sized enterprises.

- 167 “Scholars should cast out the myth of perfection, as Lucifer was cast out of heaven. In its place, we should adopt the more realistic, and helpful, conclusion that often good enough is . . . good enough” (Bambauer 2012, p. 22).
- 168 See TRIPS article 27.
- 169 Drug discovery refers to all steps commencing immediately after the identification of a disease target and includes the identification of an appropriate lead to inhibit the target and the filing of an IND covering that particular target. See discussion in section entitled “Stages of Drug Discovery and Development”.
- 170 Drug Development is defined in this article as covering all stages that commence immediately after the procurement of IND approval and covers all human clinical trials and all other steps that are required to obtain final drug regulatory approval. See discussion in section entitled “Stages of Drug Discovery and Development”.
- 171 While some studies examine the issue by considering only inventions patented by universities and public funded research institutions; see, for example, Sampat (2009), other studies take into account upstream discoveries by small biotechnology firms as well. Robert Kneller investigated 123 drugs, being conventional chemical drugs and not biologics, that had been granted priority review and approved by the US FDA from 1998 to 2007 and the patents associated with them. Of these 123 drugs, only 46% of the patents corresponding to whole drug equivalents (WDE) were attributed to the big pharmaceutical companies. Of the remaining 54%, 30% came from small biotech firms and 24% from biotechnology firms; see Kneller (2010).
- 172 It is important to note however in many cases, small biotech firms responsible for upstream inventions (or ones that acquired inventions from the discovering universities) filed the new drug application (NDA) application themselves; it is estimated that such NDA filings amounted to 60% (51 out of 86) of total filings considered in the article. The remaining 40% were divided approximately evenly between drugs that were taken through to FDA approval by another biotechnology company or by a pharmaceutical company. It is pertinent to note that the contribution of small biotech firms and universities to the total number of new drugs (and not just the most innovative drugs) approved during this time frame was much lower. See Kneller (2010).
- 173 Rasmussen notes that “[p]rior to the advent of biotechnology, the structure of the value chain of the individual pharmaceutical company was relatively self-contained. Each pharmaceutical company was fully integrated, conducting its own research, development, manufacturing and distribution of its own drugs”.
- 174 The global expenditures for health research from public funds are quite significant. It is estimated that direct expenditures from public funds accounted for about 45% of the total amount of healthcare expenditure in 2003 i.e. approximately USD 56.1 billion out of a total of USD 125.8 billion (Global Forum for Health Research, 2004).
- 175 Outterson argues that after adjustments of tax credits, etc., direct public investments in health R&D are probably significantly larger than private for-profit investments.
- 176 See University and Small Business Patent Procedures Act, 35 U.S.C. §§200–212 (1980).
- 177 As discussed in Part II, an INDA is an application seeking permission from the FDA to test a drug candidate in humans. This application contains lab-tested and other preclinical evidence to demonstrate that the drug is sufficiently effective and safe to be tested in humans. Once the INDA is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials. During this time, the FDA has an opportunity to review the INDA.
- 178 The EU follows a similar procedure to the United States, where prior to the start of human trials, the sponsor must request authorization to conduct clinical trials through a submission called a Clinical Trial Authorization (CTA). This application includes a group of scientific documents called an IMPD.
- 179 Of the total USD 802 million stated to be the average cost associated with drug discovery and development, the costs associated with the drug discovery stage amount to USD 335 million. See DiMasi (2010).

- 180 Rajan notes that the copyright regimes of many countries provide for what are commonly labelled as moral rights. The two most widely recognized moral rights are the right of attribution or paternity, ensuring that the author is acknowledged as the creator of her own work, and the right of integrity, which allows an author to protest mistreatment or abuse of her work.
- 181 Such agreement provides an opportunity for the IND/CTA applicant to insist that all its costs up to the stage of IND/CTA application have to be reimbursed by the drug originator.
- 182 Kneller found that small biotechnology firms that either made upstream discoveries or acquired such upstream discoveries from universities themselves filed the NDA in 60% of the cases (51 out of 86 drugs that were studies). The remaining 40% were cases where the drug was taken to trial by another firm, mainly those with deep pockets (Kneller, 2010).
- 183 The only significant problem with the FDA-enforced exclusivity periods is that they might permit wasteful development races in clinical research, but this problem could be avoided. If no single firm is given the exclusive rights to develop a drug, multiple competing firms could decide to run clinical trials on it at the same time in the hopes of being the first to receive FDA approval. The FDA could easily prevent such races, however, because firms cannot begin testing a drug in clinical trials without the FDA's approval, so the FDA could give its approval to only one firm (Roin, 2009, p. 568).
- 184 Trade secrets are protected in many countries, either through a statutory enactment or by way of common law. The Uniform Trade Secrets Act (USTA) in the United States defines trade secret as that which (1) derives independent economic value, actual or potential, from not being generally known to and not being readily ascertainable by proper means by, other persons who can obtain economic value from its disclosure or use and (2) is the subject of efforts that are reasonable under the circumstances to maintain its secrecy. Uniform Trade Secrets Act §1(4), 14 U.L.A. 372 (Supp. 1989).
- 185 Any breach of such contract by any of the parties thereto could, apart from attracting sanction under the relevant trade secrecy regime, also entail consequences under the relevant law of contract.
- 186 This proposition holds good for new pharmaceutical processes as well, and a trade secrecy regime could help protect such processes from unauthorized disclosure and use.
- 187 The OSDD project deploys an online social networking platform to leverage the expertise of several scientists and students across the globe and arrive at a potential cure for TB. The participants in the OSDD consist of students, scientists, researchers, academicians, institutions, corporations and anyone else committed to the ideology of discovering drugs in an open collaborative mode. See Open Source Drug Discovery, About Us, <http://www.osdd.net/about-us> [Accessed September 2011].
- 188 See *supra* notes 155–158 and accompanying text.
- 189 See Basheer and Reddy (2010).

References

- Abbott, T. A. and Vernon, J. A. (2005) 'The Cost of US Pharmaceutical Price Reductions: A Financial Simulation Model of R&D Decisions', National Bureau of Economic Research, Working Paper 11114, February [online]. Available at <<http://www.nber.org/papers/w11114.pdf>> [Accessed September 2012].
- Abramowicz, M. and Duffy, J. (2011) 'The Inducement Standard of Patentability', *Yale Law Journal*, 120(7, May), 1590–681.
- Acharya, A. and Murray, C. J. L. (1997) 'Understanding DALYs', *Journal of Health Economics*, 16(6, December), 703–30.
- Alzheimer Europe (2009) Phases of Clinical Trials [online]. Alzheimer Europe. Available at <<http://www.alzheimer-europe.org/DE/Research/Understanding-dementia-research/Clinical-trials/Phases-of-clinical-trials>> [Accessed September 2012].

- Amin, T. and Basheer, S. (2006) 'Taming of the Flu: Working Through the Tamiflu Patents in India', *Journal of Intellectual Property Rights*, 11(2, March), 113–24.
- Angell, M. (2004) *The Truth About Drug Companies: How They Deceive Us and What To Do About It*. Random House, New York.
- Arora, M. (2004) *Dictionary of Botany*, 2nd edition. Anmol Publishers Pvt. Ltd., New Delhi.
- Avance (2007) *The USD 1 Billion Drug: A Fairytale* [online]. News in Avance. Available at <http://www.avance.ch/newsletter/docs/avance_on_dimasi.pdf> [Accessed September 2012].
- Baker, B. K. (2008) 'Skepticism about the Health Impact Fund', *Health Gap* [online], 24 November. Available at <<http://www.healthgap.org/trips/bakeronHIF.htm>> [Accessed September 2012].
- Baker, D. (2005) 'The Reform of Intellectual Property', *Post-Autistic Economics Review* [online], 32(5, July). Available at <<http://www.paecon.net/PAERreview/issue32/Baker32.htm>> [Accessed September 2012].
- Bambauer, D. E. (2012) 'The Myth of Perfection', *Wake Forest Law Review* [online], 2, 22–8. Available at <http://wakeforestlawreview.com/wp-content/uploads/2012/04/Bambauer_Common-Law.pdf> [Accessed September 2012].
- Banacossa, P. & Kermani, F. (2003) 'Patent Issues and Future Trends in Drug Development', *Journal of Commercial Biotechnology*, 9(4, April), 332–38.
- Banik, M. and Kesan, J. P. (2000) 'Patents as Incomplete Contracts: Aligning Incentives for R&D Investment with Incentives to Disclose Prior Art', *Washington University Journal of Law & Policy*, 2, 23–54.
- Barton, J. H. (2003) 'Non-Obviousness', *IDEA: The Journal of Law and Technology*, 43(3), 475–508.
- Basheer, S. (2012) 'A Life Saver', *The Indian Express* [online], 15 March. Available at <<http://www.indianexpress.com/news/a-life-saver/923764/0>> [Accessed September 2012].
- Basheer, S. and Primi, A. (2009) 'The WIPO Development Agenda: Factoring in the "Technologically Proficient" Developing Countries', in DeBeer, J. (ed.), *Implementing Wipo's Development Agenda*. Wilfred Laurier University Press, Waterloo, Ontario, pp. 100–17.
- Basheer, S. and Reddy, T. P. (2008) 'The "Efficacy" of Indian Patent Law: Ironing Out the Creases under Section 3(d)', *Scripted*, 5(2, August) 234–66.
- Basheer, S. and Reddy, T. P. (2010) 'The Experimental Use Exception: A Developmental Perspective', *IDEA: The Intellectual Property Law Review*, 50(4), 831–73.
- Bell, R. A., Kravitz, R. L. and Wilkes, M. S. (2000) 'Direct-To-Consumer Prescription Drug Advertising: Trends Impact, And Implications', *Health Affairs*, 19(2, March/April), 110–28.
- Berndt, E. R. and Hurvitz, J. A. (2005) 'Vaccine Advance-Purchase Agreements for Low-Income Countries: Practical Issues', *Health Affairs*, 24(3, May), 653–65.
- Bessen, J. and Meurer, M. J. (2008a) 'Of Patents and Property', *Regulation*, 31(4), 18–26.
- Bessen, J. and Meurer, M. J. (2008b) *Patent failure: How judges, lawyers, and bureaucrats put innovators at risk*. Princeton University Press, Princeton, NJ.
- Bloom, N., Griffith, R. and Reenen, J. (2002) 'Do R&D tax credits work? Evidence from a panel of countries 1979–1997', *Journal of Public Economics*, 85(1, July), 1–31.
- Boldrin, M. and Levine, D. K. (2005) 'Innovation without Patents', *Economic and Game Theory* [online]. Available at <<http://www.dklevine.com/papers/ip.ch.4.m1004.pdf>> [Accessed September 2012].
- Bresnahan, B. W., Garrison, L. P. and Towse, A. (2007) 'Assessing a Structured, Quantitative Health Outcomes Approach to Drug Risk-Benefit Analysis', *Health Affairs*, 26(3, May), 684–95.
- Brill, A. M. (2008) *Proper Duration of Data Exclusivity for Generic Biologics: A Critique* [online], Generic Pharmaceutical Association. Available at <<http://www.gphaonline.org/sites/default/files/Brill%20Study.pdf>> [Accessed September 2012].
- Brodniewicz, Teresa and Gryniewicz, G. (2010) 'Preclinical Drug Development', *Acta Poloniae Pharmaceutica*, 67(6), 579–86.

- Brower, A. (2008) 'Is it Time To Take a Harder Look at the QALY?', *Biotechnology Healthcare*, 5(3, September-October), 47–48.
- Brown, C. L. and Thapa, S. (2007) 'Corporate scandals, the Sarbanes-Oxley Act of 2002 and equity prices', *Academy of Accounting and Financial Studies Journal*, 11(1), 83–91.
- Buchdunger, E. and Zimmercan, J. (2012) *The Story of Gleevec* [online], innovation.org. Available at <http://www.innovation.org/index.cfm/StoriesofInnovation/InnovatorStories/The_Story_of_Gleevec> [Accessed September 2012].
- Buckley, J. (2004) 'Pharmaceutical Marketing—Time for Change', *Electronic Journal of Business Ethics and Organization Studies* [online], 9(2), 4–11. Available at <http://ejbo.jyu.fi/pdf/ejbo_vol9_no2_pages_4-11.pdf> [Accessed September 2012].
- Burk, D. L. and Lemley, M. A. (2003) 'Policy Levers in Patent Law', *Virginia Law Review*, 89(7, November) 1575–696.
- Chartered Institute of Management Accountants (2005) *Official Terminology*. Chartered Institute of Management Accountants, Amsterdam.
- Coll, G. H. (1986) 'Determining Compensation for Subsequent Use of Test Data Under FIFRA: A Value Based or Cost Based Standard?', *Columbia Journal of Environmental Law*, 11(1), 193–224.
- Congressional Budget Office (2007) *Federal Support for Research and Development, Study by the Congressional Budget Office, Congress of the United States*, June [online]. Available at <<http://www.cbo.gov/sites/default/files/cbofiles/ftpdocs/82xx/doc8221/06-18-research.pdf>> [Accessed September 2012].
- Cordes, J. (1984) 'A Survey of Research Findings on the R&D Tax Credit', in Brown, K. (ed.), *The R&D Tax Credit: Issues in Tax Policy and Industrial Innovation*. American Enterprise Institute for Public Policy Research, Washington, DC, pp. 5–13.
- Cornelli, F. and Schankerman, M. (1999) 'Patent Renewals and R&D Incentives', *RAND Journal of Economics*, 30(2), 197–213.
- Cornish, W. (1983) 'The Essential Criteria for Patentability', *International Review of Industrial Property*, 14(6), 765–75.
- Cotropia, C. (2007) 'KSR and the Line Between Fact and Law', *The 271 Patent Blog* [online], 6 May. Available at <http://www.patentlyo.com/patent/2007/05/ksr_and_the_lin.html> [Accessed September 2012].
- Crossman, C., Rai, A. K., Reichman, J. H. and Uhlir, P. F. (2008) 'Pathways Across the Valley of Death: Novel Intellectual Property Strategies for Accelerated Drug Discovery', *Yale Journal of Health Policy, Law and Ethics*, 8(1), 1–36.
- Czarnitzki, D., Hanel, P. and Rosa, J. M. (2004) 'Evaluating the Impact of R&D Tax Credits on Innovation: A Microeconomic Study on Canadian Firms', ZEW- Discussion Paper 04–77, November [online]. Centre for European Economic Research. Available at <<ftp://ftp.zew.de/pub/zew-docs/dp/dp0477.pdf>> [Accessed September 2012].
- Darrow, J. J. (2007) 'The Patentability of Enantiomers: Implications for the Pharmaceutical Industry', *Stanford Technology Law Review* [online], 2. Available at <<http://stlr.stanford.edu/pdf/darrow-patentability.pdf>> [Accessed September 2012].
- Deloitte (2011) 'Global Survey of R&D Tax Incentives', *Deloitte* [online]. Available at <<http://www.investinamericasfuture.org/PDFs/Global%20RD%20Survey%20Final%20-%202011.pdf>> [Accessed September 2012].
- Dickinson, E. H. (1999) 'FDA's Role in Making Exclusivity Determinations', *Food & Drug Law Journal*, 54(2), 195–204.
- DiMasi, J. A. and Grabowski, H. G. (2007) 'The Cost of Biopharmaceutical R&D: Is Biotech Different?', *Managerial and Decision Economics*, 28(4–5), 469–79.
- DiMasi, J. A., Grabowski, H. G. and Hansen, R. W. (2003) 'The Price of Innovation: New Estimates of Drug Development Costs', *Journal of Health Economics*, 22(2), 151–85.

- DiMasi, J. A., Grabowski, H. G. and Hansen, R. W. (2008) 'Misleading Congress about Drug Development—Reply', *Journal of Health Politics, Policy & Law*, 33(2, April), 319–24.
- DiMasi, J. A., Feldman, L., Seckler, A. and Wilson, A. (2010) 'Trends in Risks Associated with New Drug Development: Success Rates for Investigational Drugs', *Clinical Pharmacology & Therapeutics*, 87(3, March), 272–77.
- Dinca, R. (2005) 'The Bermuda Triangle of Pharmaceutical Law-Is Data Protection a Lost Ship?', *The Journal of World Intellectual Property*, 8(4, July), 517–63.
- Drews, J. (2000) 'Drug Discovery: A Historical Perspective', *Science*, 287(5460), 1960–64.
- Dreyfuss, R. C. (2000) 'Are Business Method Patents Bad for Business?', *Santa Clara Computer & High Technology Law Journal*, 16(2), 263–80.
- Duffy, J. F. (2004) 'Rethinking the Prospect Theory of Patents', *University of Chicago Law Review*, 71(2), 439–510.
- Eisenberg, R. S. (2007) 'The Role of the FDA in Innovation Policy', *Michigan Telecommunications & Technology Law Journal* [online], 13(2), 345–88 (2007). Available at <<http://www.mttl.org/volthirteen/eisenberg.pdf>> [Accessed September 2012].
- Eller, B. B. (2010) 'Promoting Innovation in the Pharmaceutical Industry by Expanding the FDA's Regulatory Powers to Grant Market Exclusivity', UC Davis Legal Studies Research Paper, 19 December [online]. Available at <<http://ssrn.com/abstract=1790566>> [Accessed September 2012].
- European Medical Research Councils (EMRC) (2007) 'Present Status and Future Strategy for Medical Research in Europe'. EMRC White Paper, European Science Foundation, Strasbourg.
- Fama, E. F. and French, K. R. (1993) 'Common Risk Factors in the Returns on Stocks and Bonds', *Journal of Financial Economics*, 33(1, February), 3–56.
- Faunce, T. A. and Lexchin, J. (2007) "'Linkage' pharmaceutical ever-greening in Canada and Australia", *Australia and New Zealand Health Policy* [online], 4(8). Available at <<http://www.anzhealthpolicy.com/content/pdf/1743-8462-4-8.pdf>> [Accessed September 2012].
- Fauver, C. M. (1988) 'Compulsory Licensing in the United States: An Idea Whose Time Has Come', *North-western Journal of International Law & Business*, 8(3), 666–85.
- Fellmeth, A. X. (2004) 'Secrecy, Monopoly and Access to Pharmaceuticals in International Trade Law: Protection of Marketing Approval Data under the TRIPS Agreement', *Harvard International Law Journal*, 45(2), 443–502.
- Financial Express (2005) 'Roche sub-licences Tamiflu to Hetero Drugs', *Financial Express* [online]. Available at <<http://www.financialexpress.com/news/roche-sublicenses-tamiflu-to-hetero-drugs/129542/>> [Accessed September 2012].
- Fink, C. and Reichenmiller, P. (2006) 'Tightening TRIPS: Intellectual Property Provisions of U.S. Free Trade Agreements', in Newfarmer, R. (ed.), *Trade, Doha and Development*. The World Bank, Washington, DC, pp. 285–300.
- Fisher, W. (2001) 'Theories of Intellectual Property', in Munzer, S. R. (ed.) *New Essays in the Legal and Political Theory of Property*. Cambridge University Press, Cambridge, pp. 168–200.
- Fisher, W. and Syed, T. (2008) 'A Prize System As a Partial Solution to the Health Crisis in The Developing World', October [online]. Available at <http://www.law.berkeley.edu/files/Fisher_Prizes12.pdf> [Accessed September 2012].
- Flower, D. R. (2002) 'Molecular Informatics: Sharpening Drug Design's Cutting Edge', in Darren Flower (ed.), *Drug Design: Cutting Edge Approaches*. The Royal Society of Chemistry, Cambridge, pp. 1–52.
- Fox, M. (2010) 'US takes step to Government Drug Development Center', *Reuters* [online], 7 December. Available at <<http://www.reuters.com/article/2010/12/07/us-usa-institute-idUSTRE6B66ZG20101207>> [Accessed September 2012].

- Fryback, D. G., Gold, M. R. and Stevenson, D. (2002) 'HALYs and QALYs and DALYs, Oh My: Similarities and Differences in Summary Measures of Population Health', *Annual Review of Public Health*, 23, May, 115–34.
- Furrow, M. E. (2008) 'Analyzing The Laws, Regulations, and Policies Affecting FDA-Regulated Products: Pharmaceutical Patent Life-Cycle Management After *KSR v. Teleflex*', *Food & Drug Law Journal*, 63(1), 275–320.
- Gagnon, M. and Lexchin, J. (2008) 'The Cost of Pushing Pills: A New Estimate of Pharmaceutical Promotion Expenditures in the United States', *PLOS Medicine*, 5(1, January), 0029–33.
- Gibbons, R. G. and Vogel, B. J. (2007) 'The Increasing Importance of Trade Secret Protection in the Biotechnology, Pharmaceutical and Medical Device Fields', *Journal of the Patent and Trademark Office Society*, 89(4, April), 261–86.
- Gitter, D. M. (2008) 'Innovators and Imitators: An Analysis of Proposed Legislation Implementing an Abbreviated Approval Pathway for Follow-On Biologics in the United States', *Florida State University Law Review*, 35(3), 555–626.
- Global Forum for Health Research (2004) *Monitoring Financial Flows for Health Research*, Vol. 2, Global Forum for Health Research, Geneva [online]. Available at <http://announcementsfiles.cohred.org/gfhr_pub/assoc/s14826e/s14826e.pdf> [Accessed September 2012].
- Golec, J. H. and Vernon, J. A. (2007) 'Financial Risk in the Biotechnology Industry', National Bureau of Economic Research, Working Paper 13604, November [online]. Available at <<http://www.nber.org/papers/w13604.pdf>> [Accessed September 2012].
- Grabowski, H. (2002) 'Patents and New Product Development in the Pharmaceutical and Biotechnology Industries', *Journal of International Economic Law*, 5(4, December), 849–60.
- Hall, B. H. (2007) 'Patents and Patent Policy', *Oxford Review of Economic Policy*, 23(4), 568–87.
- Hall, B. H. and Reenen, J. (2000) 'How Effective Are Fiscal Incentives for R&D? A Review of the Evidence', *Research Policy*, 29(4–5, April), 449–69.
- Harrington, S. E. (2012) 'Cost of Capital for Pharmaceutical, Biotechnology, and Medical Device Firms', in P. Danzon and S. Nicholson (eds) (2012) *The Handbook of the Economics of the Biopharmaceutical Industry*. Oxford University Press: New York, pp. 75–99.
- Harris, G. (2002) 'Prilosec's Maker Switches Users To Nexium, Thwarting Generics', *Wall Street Journal* [online], 6 June. Available at <<http://www.chelationtherapyonline.com/technical/p36.htm>> [Accessed September 2012].
- Harris, J. (1987) 'QALYfying the Value of Life', *Journal of Medical Ethics*, 13(3, September), 117–23.
- Harris, J. (2005) 'It's Not NICE to Discriminate', *Journal of Medical Ethics*, 31(7, July), 373–75.
- Health Impact Fund (HIF) (2012) *A Proposal of Incentives for Global Health: Proposal & Pilot* [online], Health Impact Fund. Available at <<http://www.healthimpactfund.org/pilot.html>> [Accessed September 2012].
- Heled, Y. (2012) 'Patents vs. Statutory Exclusivities in Biological Pharmaceuticals—Do We Really Need Both?', *Michigan Telecommunications & Technology Law Journal* [online], 18(2), 419–79. Available at <<http://www.mttl.org/voleighteen/heled.pdf>> [Accessed September 2012].
- Heller, M. A. and Eisenberg, R. S. (1998) 'Can Patents Deter Innovation? The Anti-commons in Biomedical Research', *Science*, 280(5364, May), 698–701.
- Henderson, J. and Smith, J. (2002) 'Academia, Industry and the Bayh-Dole Act: An Implied Duty to Commercialize', Center for Integration of Medicine and Innovative Technology [online], October. Available at <http://www.cimit.org/news/regulatory/coi_part3.pdf> [Accessed September 2012].
- Hollis, A. (2005) *An Efficient Reward System for Pharmaceutical Innovation*, 17 January [online]. Available at <<http://www.who.int/intellectualproperty/news/Submission-Hollis6-Oct.pdf>> [Accessed September 2012].

- Hollis, A. (2008) 'The Health Impact Fund: A Useful Supplement to the Patent System?', *Public Health Ethics*, 1(2), 124–33.
- Hollis, A. and Pogge, T. (2008) *The Health Impact Fund: Making New Medicines Accessible for All*. Incentives for Global Health, New Haven, CT.
- Hollis, A., Peterson, M. and Pogge, T. (2010) 'A Critique in Need of Critique', *Public Health Ethics*, 3(2), 178–85.
- Howells, J. (2008) 'Patents and Downstream Innovation Suppression—Facts or Fiction?—A Critique of the Use of Historical Sources in Support of the Thesis that Broad Patent Scope Enables the Suppression or Hindrance of Downstream Useful-Technology Development', Centre for Organizational Renewal and Evolution, Working Paper-2008–01 [online]. Available at <http://www.pucsp.br/icim/ingles/downloads/pdf_proceedings_2008/11.pdf> [Accessed September 2012].
- Hubbard, T. and Love, J. (2009) 'Prizes for Innovation in New Medicines and Vaccines', *Annals of Health Law*, 18(2), 155–86.
- Huskamp, H. A. (2006) 'Prices, Profits and Innovation: Examining Criticisms of the Value of New Psychotropic Drugs', *Health Affairs*, 25(3, May), 635–46.
- Institute of Community Medicine (2012) Seminar on *Rational Use of Drugs* [online], Institute of Community Medicine, Government of Tamil Nadu. Available at <<http://www.icm.tn.gov.in/seminar/RATHLSYS.htm>> [Accessed September 2012].
- International Federation of Pharmaceutical Manufacturers Associations (IFPMA) (2005) *A Review of Existing Data Exclusivity Legislation In Selected Countries* [online], IFPMA. Available at <http://www.ifpma.org/documents/NR2799/DataExclusivity_2005.pdf> [Accessed September 2012].
- Jayadev, A. and Stiglitz, J. (2010) 'Medicine for Tomorrow: Some Alternative Proposals to Promote Socially Beneficial Research and Development in Pharmaceuticals', *Journal of Generic Medicines*, 7(3), 217–26.
- Johnson, J. A. (2010) 'FDA Regulation of Follow-On Biologics', Congressional Research Service Report for the Congress, [online]. Available at <http://www.primaryimmune.org/advocacy_center/pdfs/health_care_reform/Biosimilars_Congressional_Research_Service_Report.pdf> [Accessed September 2012].
- Junod, V. (2004) 'Drug Marketing Exclusivity under United States and European Union Law', *Food & Drug Law Journal*, 59(4), 479–518.
- Kairys, D. (1984) 'Law and Politics', *George Washington Law Review*, 52(2, January), 243–62.
- Kanavos, P. (2001) 'Overview of Pharmaceutical Pricing Reimbursement Regulation in Europe', LSE Health [online]. Available at <http://www.eco.uc3m.es/servicios/sesam/actividades/jornada_legislacion/DOC%209%20EMEARoadMap.pdf> [Accessed September 2012].
- Kennedy, D. (1976) 'Form and Substance in Private Law Adjudication', *Harvard Law Review*, 89(8, June) 1685–778.
- Kingston, W. (1987) 'The Unexploited Potential of Patents', in William Kingston (ed.), *Direct Protection Of Innovation*. Kluwer Academic Publishers, Boston, MA, pp. 1–32.
- Kitch, E. W. (1977) 'The Nature and Function of the Patent System', *Journal of Law & Economics*, 20(2, October), 265–90.
- Kneller, R. (2010) 'The Importance of New Companies for Drug Discovery: Origins of a Decade of New drugs', *Nature Reviews Drug Discovery*, 9(11, November), 867–82.
- Koh Jun, O. (2012) 'Rare Diseases—A Sustainable Model for the Pharmaceutical Industry', Glaxo-SmithKline Rare Diseases Competition [online]. Available at <http://www.gsk.com/rare-diseases/papers/winner-3_koh-jun.pdf> [Accessed September 2012].
- Landes, W. M. and Posner, R. A. (2003) *The Economic Structure of Intellectual Property Law*. Harvard University Press, Cambridge, MA.
- Lane, B. G. (1987) 'A Proposal to View Patent Claim Non-obviousness From the Policy Perspective of Federal Rule of Civil Procedure 52(a)', *University of Michigan Journal of Law Reform*, 20(4), 1157–214.

- Lanjouw, J. O. (2003) 'Intellectual Property and the Availability of Pharmaceuticals in Poor Countries', in: A. B. Jaffe, J. Lerner and S. Stern (eds), *Innovation Policy and the Economy*, Vol. 3, Massachusetts Institute of Technology Press, Cambridge, MA, pp. 91–130.
- Lemley, M. A. (2001) 'Rational Ignorance at the Patent Office', *Northwestern University Law Review*, 95(4), 1495–532.
- Lemley, M. A. (2005) 'Property, Intellectual Property, and Free Riding', *Texas Law Review*, 83(4, March) 1031–76.
- Lemley, M. A. and Weiser, P. J. (2007) 'Should Property or Liability Rules Govern Information', *Texas Law Review*, 85(4, March), 783–842.
- Levitt J. A. and Kelsey, J. V. (1993) 'The Orphan Drug Regulations and Related Issues', *Food and Drug Law Journal*, 48(4), 525–33.
- Lewis, T. R., Reichman, J. H. and So, A. D. (2007) 'The Case for Public Funding and Public Oversight of Clinical Trials', *Economists' Voice*, 4(1, January), 1–4.
- Li, P., Sakharkar, M. K., Zhong, Z. and Sakharkar, K. R. (2008) 'Quantitative Analysis on the Characteristics of Targets with FDA Approved Drugs', *International Journal of Biological Sciences*, 4(1), 15–22. Available at <<http://www.biolsci.org/v04p0015.pdf>> [Accessed September 2012].
- Light, D. W. (2007) 'Misleading Congress About Drug Development', *Journal of Health Politics, Policy & Law*, 32(5, October), 895–913.
- Light, D. W. and Walburton, R. (2011) 'Demythologizing the High Costs of Pharmaceutical Research', *BioSocieties* [online], 1–17. Available at <http://www.pharmamyths.net/files/Biosocieties_2011_Myths_of_High_Drug_Research_Costs.pdf> [Accessed September 2012].
- Love, J. (2003) 'A New Trade Framework for Global Healthcare R&D', Workshop Hosted by the Program on Science, Technology, and Global Development, The Earth Institute at Columbia University, and the Consumer Project on Technology, Washington, DC, 4 December.
- Love, J., Sanjuan, J. R. and Weissman, R. (2006) 'A Cost Sharing Model to Protect Investments in Pharmaceutical Test Data', Consumer Project on Technology Policy Brief No. 1, 18 May [online]. Available at <<http://www.cptech.org/publications/policybrief-no1-cost-sharing.pdf>> [Accessed September 2012].
- Machlup, F. (1958) 'An Economic Review of the Patent System. Study of the Subcommittee on Patents', Trademarks & Copyrights of the Committee on the Judiciary, United States Senate, 85th Congress, 2nd Session. Committee Print, Washington, DC.
- Macmillan Dictionary Thesaurus (2011) 'In Vitro Definition', *Macmillan Dictionary Thesaurus*. Available at <http://www.macmillandictionary.com/thesaurus/british/in-vitro#in-vitro_3> [Accessed September 2012].
- Mandel, G. N. (2008) 'The Non-Obvious Problem: How the indeterminate Non-Obvious Standard Produces Excess Patent Grants', *U.C. Davis Law Review*, 42(1, November), 57–128.
- Mansfield, E. (1986) 'Patents and Innovation: An Empirical Study', *Management Science*, 32(2), 173–81.
- Maurer, S. (2005a) 'The Right Tool(s): Designing Cost-Effective Strategies for Neglected Disease Research', Commission on Intellectual Property Rights, Innovation and Public Health Studies [online], 29 March. Available at <<http://www.who.int/intellectualproperty/studies/S.Maurer.pdf>> [Accessed September 2012].
- Maurer, S. (2005b) 'When Patents Fail: Finding New Drugs for the Developing World', International Conference on Pharmaceutical Innovation, Taipei, China, 27 May [online]. Available at <http://gspp.berkeley.edu/iths/Maurer_WhenPatentsFail.pdf> [Accessed September 2012].
- Mazzoleni, R. and Nelson, R. R. (1998) 'Economic Theories About the Benefits and Costs of Patents', *Journal of Economic Issues*, 32(4, December), 1031–52.

- Merges, R. P. (1992) 'Uncertainty and the Standard of Patentability', *Berkeley Technology Law Journal* [online], 7(1, May), 1–70. Available at <<http://www.btlj.org/data/articles/vol7/Merges.pdf>> [Accessed September 2012].
- Merges, R. P. and Nelson, R. R. (1990) 'The Complex Economics of Patent Scope', *Columbia Law Review*, 90(4, May), 839–916.
- Merrill, R. A. (1996) 'The Architecture of Government Regulation of Medical Products', *Virginia Law Review*, 82(8, November), 1753–866.
- Minssen, T. (2010) 'Meanwhile on The Other Side of The Pond: Why Biopharmaceutical Inventions That Were "Obvious To Try" Still Might Be Non-Obvious—Part I', *Journal of Intellectual Property*, 9(2), 60–131.
- Morgan, M. R. (2010) 'Regulation of Innovation under Follow-on Biologics Legislation: FDA Exclusivity as an Efficient Incentive Mechanism', *The Columbia Science & Technology Law Review* [online], 11(July), 93–117. Available at <<http://www.stlr.org/html/volume11/morgan.pdf>> [Accessed September 2012].
- Moses III, H., Dorsey, E. R., Matheson, D. H. M. and Thier, S. O. (2005) 'Financial Anatomy of Biomedical Research', *Journal of American Medical Association*, 294(11, September), 1333–42.
- Moss, G., Jones, M. and Lundie-Smith, R. (2010) 'Just How 'Anti-Patent' Are the UK Courts?', *Journal of Intellectual Property Law and Practice*, 5(3), 148–57.
- Mossinghoff, G. J. (1999) 'Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process', *Food & Drug Law Journal*, 54(2), 187–94.
- Mullally, K. C. (2010) 'Legal (Un)certainty, Legal Process, and Patent Law', *Loyola of Los Angeles Law Review*, 43(3), 1109–60.
- National Academies Committee on Science, Engineering and Public Policy (2007) 'What Actions Should America Take in Economic and Technology Policy to Remain Prosperous in the 21st Century?', in N. Grossblatt (ed.), *Rising Above the Gathering Storm*. The National Academies Press, Washington, DC, pp. 182–203.
- National Institutes of Health (NIH) (2008), Biennial Report of the Director FY2008 & 2009- Clinical and Translational Research [online], NIH. Available at <<http://report.nih.gov/biennialreport/ViewSection.aspx?sid=18&cid=3>> [Accessed on 20 September 2012].
- National Institutes of Health (NIH) (2012) *About NIH: NIH Budget* [online], National Institutes of Health. Available at <<http://www.nih.gov/about/budget.htm#note>> [Accessed September 2012].
- Novartis Pharmaceuticals Corporation (2012) *Prescribing Information* [online], Novartis. Available at <http://www.pharma.us.novartis.com/product/pi/pdf/gleevec_tabs.pdf> [Accessed September 2012].
- Open Source Drug Discovery (OSDD) (2011) *About Us* [online], Open Source Drug Discovery. Available at <<http://www.osdd.net/about-us>> [Accessed September 2012].
- Orlhac, T. (1990) 'The New Canadian Pharmaceutical Compulsory Licensing Provisions or How to Jump Out of the Frying Pan and into the Fire', Robic Publications [online]. Available at <<http://www.robic.ca/admin/pdf/514/167E-TO.pdf>> [Accessed September 2012].
- Outterson, K. (2008) 'Should Access to Medicines and TRIPS Flexibilities be Limited to Specific Diseases?', *American Journal of Law and Medicine*, 34(2–3), 279–301.
- Parchomovsky, G. and Wagner, R. P. (2005) 'Patent Portfolios', *University of Pennsylvania Law Review*, 154(1, November), 1–78.
- Pasquale, F. (2011) 'After Makena: Could a Risk Corridors Approach Balance Incentives and Access?', *Health Reform Watch* [online], 30 March. Available at <<http://www.healthreformwatch.com/2011/03/30/after-makena-could-a-risk-corridors-approach-balance-incentives-and-access/>> [Accessed September 2012].
- Petherbridge, L. (2010) 'On the Development of Patent Law', *Loyola of Los Angeles Law Review*, 43(3), 893–944.

- Pharmaceutical Research and Manufacturers of America (PhRMA) (2010) *Pharmaceutical Industry Profile 2010* [online], Pharmaceutical Research and Manufacturers of America. Available at <http://www.phrma.org/sites/default/files/159/profile_2010_final.pdf> [Accessed September 2012].
- Pharmaceutical Research and Manufacturers of America (PhRMA) (2008) *The Facts About Pharmaceutical Marketing and Promotion*. PhRMA, Washington, DC [online]. Available at <http://www.phrma.org/sites/default/files/159/marketing_and_promotion_facts_071108_final.pdf> [Accessed September 2012].
- Pharmaceutical Research and Manufacturers of America (PhRMA) (2004) 'Pharmaceutical Price Controls and other Market Access Barriers in Developed Countries', Submission by PhRMA to the United States Department of Commerce, 1 July [online]. Available at <<http://ita.doc.gov/td/health/phRMA/phRMA%20-%20ANNEX%20A.pdf>> [Accessed September 2012].
- Phillips, C. (2009) What Is a QALY? [online], What is ...? Series. Available at <http://www.whatisseries.co.uk/whatis/pdfs/What_is_a_QALY.pdf> [Accessed September 2012].
- Pila, J. (2003) 'Bound Futures: Patent Law and Modern Biotechnology', *Boston University Journal of Science and Technology Law*, 9(2), 326–78.
- Public Citizen (2001) 'Rx R&D Myths: The Case against the Drug Industry's R&D "Scare Card"', Public Citizen's Congress Watch [online]. Available at <<http://www.citizen.org/documents/rdmyths.pdf>> [Accessed September 2012].
- Public Citizen (2010) Rebuttals to PhRMA Responses to the Public Citizen Report, "Rx R&D Myths: The Case Against The Drug Industry's R&D 'Scare Card'" [online], Public Citizen. Available at http://www.citizen.org/congress/article_redirect.cfm?ID=6514 [Accessed September 2012].
- Rader, R. A. (2005) 'Biopharmaceutical Terminology, Part I: What Is a Biopharmaceutical?' Is the Industry Losing its Identity?, *Bioexecutive International* [online] (March), 60–5. Available at <http://www.biopharma.com/bioexec_pt1.pdf> [Accessed September 2012].
- Rajfer, J., Aronson, W. J., Bush, P. A., Dorey, F. J. and Ignarro, L. J. (1992) 'Nitric Oxide as a Mediator of Relaxation of the Corpus Cavernosum in Response to Nonadrenergic, Noncholinergic Neurotransmission', *New England Journal of Medicine*, 326(2, January), 90–4.
- Rajan, M. T. S. (2002) 'Moral Rights and Copyright Harmonisation: Prospects for an 'International Moral Right''?', Paper presented at the 17th BILETA Annual Conference, Free University, Amsterdam, 5–6 April.
- Rasmussen, B. (2007) 'Response of Pharmaceutical Companies to Biotechnology: Structure and Business Model', Centre for Strategic Economic Studies, Working Paper No. 33, August [online]. Available at <http://www.cfses.com/documents/pharma/33-Pharmaceutical_Business_Models_Rasmussen.pdf> [Accessed September 2012].
- Raubitschek, J. (2005) 'Responsibilities Under the Bayh Dole Act', *Journal of the Patent and Trademark Office Society*, 87(4, April), 311–18.
- Reichman, J. H. (2000) 'Of Green Tulips and Legal Kudzu: Repackaging Rights in Subpatentable Innovation', *Vanderbilt Law Review*, 53(6, November), 1743–98.
- Reichman, J. H. (2009) 'Rethinking The Role Of Clinical Trial Data In International Intellectual Property Law: The Case For A Public Goods Approach', *Marquette Intellectual Property Law Review*, 13(1), 1–68.
- Rich, G. S. (2004) 'Why and How Section 103 Came to Be', *Federal Circuit Bar Journal*, 14(1), 181–192.
- Rigamonti, C. P. (2006) 'Deconstructing Moral Rights', *Harvard International Law Journal*, 47(2), 353–412.
- Rigamonti, C. P. (2007) 'The Conceptual Transformation of Moral Rights', *American Journal of Comparative Law*, 55(1), 67–122.
- Roin, B. (2007) *Pharmaceutical Innovation and the Limits of the Patent System* [online]. Available at <<http://www.law.harvard.edu/faculty/workshops/climenko/Roin.pdf>> [Accessed September 2011].

- Roin, B. N. (2009) 'Unpatentable Drugs and the Standards of Patentability', *Texas Law Review*, 87(3, February), 503–70.
- Russo, B. (2004) 'A cost-benefit analysis of R&D tax incentives', *Canadian Journal of Economics*, 37(2, May), 313–35.
- Sampat, B. N. (2009) 'Academic Patents and Access to Medicines in Developing Countries', *American Journal of Public Health*, 99(1), 9–17.
- Schacht, W. H. and Thomas, J. R. (2002) *Pharmaceutical Patent Term Extensions: A Brief Explanation*, Congressional Research Service Report for Congress [online]. Available at <<http://www.law.umaryland.edu/marshall/crsreports/crsdocuments/RS21129.pdf>> [Accessed September 2012].
- Scherer, F. M. (1980) *Industrial Market Structure and Economic Performance*, 2nd edition. Rand-McNally, Chicago, IL.
- Scherer, F. M. (2007) 'Pharmaceutical Innovation', AEI–Brookings Joint Center, Working Paper No. 07–19.
- Schwartzman D. (1976) *Innovation in the Pharmaceutical Industry*. Johns Hopkins University Press, Lanham, MD.
- Scotchmer, S. (2004) 'Patent Quality, Patent Design, and Patent Politics', Remarks before the European Patent Office as a member of the Advisory Group, European Patent Office, Munich 10 December [online]. Available at <http://socrates.berkeley.edu/~scotch/Scotchmer_epo.pdf> [Accessed September 2012].
- Sichelman, T. (2010) 'Commercializing Patents', *Stanford Law Review*, 62(2, January), 341–412.
- Silberman S. (2009) 'Placebos Are Getting More Effective. Drugmakers Are Desperate to Know Why', *Wired Magazine* [online], 17 September. Available at <http://www.wired.com/medtech/drugs/magazine/17-09/ff_placebo_effect?currentPage=all> [Accessed September 2012].
- Solum, L. B. (1987) 'On the Indeterminacy Crisis: Critiquing Critical Dogma', *University of Chicago Law Review*, 54(2), 462–503.
- Staton, T. (2011) 'Senators Demand FTC Probe of KV's Makena Pricing' *Fierce Pharma* [online], 21 March. Available at <<http://www.fiercepharma.com/story/senators-demand-ftc-probe-kvs-makena-pricing/2011-03-21#ixzz1Jg9U25dc>> [Accessed September 2012].
- Stief, C. G. (2000) 'Phosphodiesterase Inhibitors in the Treatment of Erectile Dysfunction', *Drugs of Today*, 36(2–3, February/March), 93–100.
- Su, Y., Vanhaverbeke, W. and Wu, F-S. (2010) 'How Small Firms Can Benefit From Open Innovation? Evidence From Taiwanese Biotechnology Firms', Paper presented at the Summer Conference 2010 on 'Opening Up Innovation: Strategy, Organization and Technology' at Imperial College London Business School, London, 16–18 June.
- Swidey, N. (2002) 'The Costly Case of the Purple Pill', *Boston Globe Magazine* [online], 17 November. Available at <<http://home.comcast.net/~neilswidey/pill.htm>> [Accessed September 2012].
- Thomas, J. R. (2009) 'Patent "Evergreening": Issues in Innovation and Competition'. Congressional Research Service Report for the Congress [online]. Available at <http://ipmall.info/hosted_resources/crs/R40917_091113.pdf> [Accessed September 2012].
- Thomas, P. (2000) *Trees: Their Natural History*. Cambridge University Press, Cambridge.
- Torrance, A. W. and Tomlinson, B. (2009) 'Patents and the Regress of Useful Arts', *Columbia Science & Technology Law Review*, 10(May), 130–68.
- Tufts Centre for Study of Drug Development (2001) 'Backgrounder: A Methodology for Counting Costs for Pharmaceutical R&D', Tufts Centre for Study of Drug Development [online]. Available at <<http://csdd.tufts.edu./NewsEvents/RecentNews.asp?newsid=5>> [Accessed September 2012].
- Tushnet, M. V. (1983) 'Following the Rules Laid Down: A Critique of Interpretivism and Neutral Principles', *Harvard Law Review*, 96(4, February), 781–827.
- Tzeng, L. (2010) 'Follow-on Biologics, Data Exclusivity and the FDA', *Berkeley Technology Law Journal*, 25(1, October), 135–58.

- U.S. Congress, Office of Technology Assessment (OTA) (1993) *Pharmaceutical R&D: Costs, Risks and Rewards, OTA-H-522*. U.S. Government Printing Office, Washington, DC.
- United States Senate (2000) 'The Benefits of Medical Research and the Role of the NIH', United States Senate [online], 17 May. Available at <http://www.faseb.org/portals/0/pdfs/opa/2008/nih_research_benefits.pdf> [Accessed September 2012].
- US Food and Drug Administration (FDA) (2011a) 'The Beginnings: Laboratory and Animal Studies', *Information for Consumers (Drugs)* [online], US Food and Drug Administration. Available at <<http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143475.htm>> [Accessed September 2012].
- US Food and Drug Administration (FDA) (2011b) *Investigational New Drug (IND) Application* [online], US Food and Drug Administration. Available at <<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm>> [Accessed September 2012].
- US Food and Drug Administration (FDA) (2011c) *Inside Clinical Trials: Testing Medical Products in People* [online], US Food and Drug Administration. Available at <<http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143531.htm>> [Accessed September 2012].
- US Food and Drug Administration (FDA) (2011d) *FDA Statement on Makena* [online], US Food and Drug Administration, Available at <<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm249025.htm>> [Accessed September 2012].
- Vaver, D. (2003) 'Invention in Patent Law: A Review and a Modest Proposal', *International Journal of Law and Information Technology*, 11(3), 287–307.
- Weiss, J. (2010) 'Medical Marketing in the United States: A Prescription for Reform', *George Washington Law Review*, 79(1), 260–92.
- Wood, L. F. and Foote, M. (eds) (2009) *Targeted Regulatory Writing Techniques: Clinical Documents for Drugs and Biologics*. Birkhäuser Verlag, Basel.