

RESTRUCTURING INCENTIVES FOR PHARMACEUTICAL INNOVATION

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The Agreement on the Trade Related Aspects of Intellectual Property Rights (“TRIPS”) was a landmark event in the efforts for global harmonization of intellectual property standards. The TRIPS marked a significant departure from the status quo in many member countries that had till then denied product patents to pharmaceuticals. Though developing countries have since amended their patent laws to comply with the TRIPS mandate, the process of reform is ongoing. An emerging area of reform is to restrict the patentability of pharmaceuticals that do not offer therapeutic benefits as compared to known drugs. This article analyzes whether reform with respect to such drugs is warranted and if so, whether patent law is the appropriate model for such reforms. The paper concludes that while a balanced restructuring of incentives in pharmaceutical innovation is needed, the patent system is not an appropriate model for carrying out these reforms.

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I. INTRODUCTION

Over the past two decades, developing countries have reformed their patent regimes to bring it in compliance with the TRIPS, while using the flexibilities incorporated therein. An emerging issue for reform has been the denial of patentability to specific categories of pharmaceutical innovation that are often referred to as “me-too” drugs¹ and “follow-on drugs”.² Legislation, specifically directed to these categories

¹ Since the literature on this subject attributes varying meaning to the term “me-too” drug, it is important to clarify the terminology used in this paper. For the purposes of this article, the term “me-too” drug has been used to signify a drug that is the chemical analogue of a drug already on the market. In other words, the term ‘me-too’ drug has been used for a new entrant in a therapeutic class that had already been defined by an earlier drug, which was the first in its class to receive marketing approval.

² For the purposes of this article, the term “follow-on” drugs signifies drugs obtained through the process of incremental innovation, i.e., from follow-up R&D essentially based on that of an existing product. Examples of follow-on products include salts, esters, ethers, enantiomers, polymorphs etc. of existing drugs.

of pharmaceutical innovation, has been passed by India,³ Philippines,⁴ and Argentina,⁵ and is currently being considered by Brazil,⁶ and South Africa.⁷ The United Nations Conference on Trade and Development has also proposed reforms to be adopted by developing countries for addressing these issues⁸. At the same time, developed countries such as the United States are trying to thwart such attempts at reform through the use of a multilateral free trade agreement.⁹ This article examines two aspects of this issue: first, the threshold question – Is there a need for reform to reduce the incentives of pharmaceutical firms for the development of “me-too” drugs and “follow on drugs”? Second, if such reform is needed, is the patent system the appropriate model for such reform?

Part II of this article focuses on the debate around “me-too” drugs, critically examining arguments both in favour of and against the development and protection of “me-too” drugs. Part III carries out a similar analysis with respect to the development and protection of “follow-on” drugs. Part IV proposes solutions for restructuring incentives for pharmaceutical innovation. Part V examines the appropriateness of incorporating these solutions in different systems of incentives, with particular emphasis on the patent system.

The aim of this article is modest: It seeks to identify whether the current status of “me-too” drugs and “follow-on” drugs merit a restructuring of incentives and, if so, to determine whether one of the solutions, namely, patent protection is appropriate. While there exist alternative models for realigning incentives in pharmaceutical innovation, this paper will only examine them briefly.

³ See § 3(d), The Patents Act, No. 39 of 1970, INDIA CODE (1993) (as amended by The Patents (Amendment) Act, No. 15 of 2005, INDIA CODE (1993)).

⁴ See INTELLECTUAL PROPERTY CODE, § 22, Rep. Act 8293, as amended by Universally Accessible Cheaper and Quality Medicines Act, Rep. Act No. 9502, (2008)(Phil).

⁵ See *Guidelines for Patentability Examination of Patent Applications Directed to Chemical and Pharmaceutical Inventions*, Joint Resolution 118/2012, 546/2012 and 107/2012 (Patents And Utility Models), Ministry of Industry, Ministry of Health & National Industrial Property Institute, (May 8, 2012) [“*Guidelines for Patentability Examination of Patent Applications Directed to Chemical and Pharmaceutical Inventions*”].

⁶ See *Brazil's Patent Reform: Innovation towards National Competitiveness*, Centre for Strategic Studies and Debates (2013) available at http://infojustice.org/wp-content/uploads/2013/09/Brazilian_Patent_Reform.pdf

⁷ See Draft National Policy on Intellectual Property, Department of Trade and Industry, Republic of South Africa available at www.gov.za/documents/download.php?f=198116.

⁸ See United Nations Conference on Trade and Development, *Using Intellectual Property Rights to Stimulate Pharmaceutical Production in Developing Countries: A Reference Guide*, 2011 available at http://unctad.org/en/Docs/diaepcb2009d19_en.pdf [“UNCTAD REFERENCE GUIDE”].

⁹ See Draft text of the Trans Pacific Partnership Agreement art. QQ.E.1, Nov. 13, 2013 available at <https://wikileaks.org/tpp/>.

II. “ME – TOO” DRUGS: DEFINING THE PROBLEM

Pharmaceutical companies adopt several strategies in their search for new lead compounds. For instance, they may choose to screen molecules invented through original efforts of chemical research and test them for therapeutic effects or they may capitalize on the known effects of natural substances and exploit it for drug development for humans. However, the strategy that has developed as the most popular means of drug development is synthesis of chemical analogues of existing active molecules with known therapeutic effects.¹⁰ It is this strategy that has led to the proliferation of “me-too” drugs.

The development of “me-too” drugs by the pharmaceutical industry has been the subject of intense debate, with academicians and representatives from the pharmaceutical industry weighing in on both sides of the issue.¹¹ Those arguing against the development of “me-too” drugs primarily suggest that pharmaceutical companies expend resources excessively in their development, neglecting other, more innovative strategies for drug discovery and development. Those arguing in favour of the development of “me-too” drugs suggest that such drugs often exhibit superior therapeutic effectiveness and thus their synthesis represents a valid strategy for drug development. This section reviews arguments both for and against the development of “me-too” drugs.

A. Arguments in favour of the development of “me-too” drugs

The arguments for “me-too” drugs can be categorized into four broad categories namely (i) they present therapeutic alternatives, (ii) they may be superior to first-in-class drugs, (iii) they represent incremental innovation and may lead to discovery of new properties and (iv) they provide price competition.

¹⁰ See Camille Wermuth, *Strategies in the Search for New Lead Compound Hypothesis or Original Working Hypothesis*, in THE PRACTICE OF MEDICINAL CHEMISTRY 125, 126 (Wermuth ed., 3rd ed., 2011) [“Wermuth”].

¹¹ See generally Aidan Hollis, *Me-too Drugs: Is There a Problem?*, (Dec. 13, 2004), http://www.who.int/intellectualproperty/topics/ip/Me-tooDrugs_Hollis1.pdf [“Hollis”]; Arnold Relman & Marcia Angell, *America’s Other Drug Problem*, THE NEW REPUBLIC 27, Dec. 16, 2002, available at www.commercialalert.org/relmanangell.pdf [“Relman & Angell”]; Marcia Angell, *The Truth About Drug Companies: How They Deceive Us and What to Do About It* (2005) [“ANGELL”]; see Wertheimer et al., *Too many drugs? The Clinical And Economic Value Of Incremental Innovations*, in INVESTING IN HEALTH: THE SOCIAL AND ECONOMIC BENEFITS OF HEALTH CARE INNOVATION 77, 86 (Farquhar, Summers et al eds., vol. 14, 2001) [“Wertheimer”]; Joseph DiMasi & Cherie Paquette, *The Economics of Follow-on Drug Research and Development: Trends in Entry Rates and the Timing of Development*, 22 Supp. 2 PHARMACO ECON. 1, 11 (2004) [“DIMASI & PAQUETTE”]; John LaMattina, *Drug truths: Dispelling The Myths About Pharma R&D* (2009) [“LAMATTINA”].

First, “me-too” drugs increase therapeutic options and exhibit therapeutic superiority. The mechanism of drug action in humans is a complex science, one that grapples with a host of variables attributable to the heterogeneity of the human population. Consequently, a one-size-fits-all approach is inappropriate, as drugs suitable for a particular sub-class of patients often turn out to be ineffective or unsafe for patients in another sub-class. In these circumstances, “me-too” drugs offer viable therapeutic alternatives and allow treatment of patients with different needs.¹² This hypothesis is drawn from studies conducted on antidepressants falling within the same drug class (serotonin re-uptake inhibitors).¹³

Secondly, proponents further argue that “me-too” drugs are often therapeutically superior compared to first-in-class drugs,¹⁴ and that, in fact, pharmaceutical firms never pursue drug candidates that are likely to be therapeutically identical to drugs already in the market.¹⁵ Statins, a class of drugs used to lower cholesterol levels, is an oft-quoted example in support of this argument. The first statin was introduced in the market in 1987 and by the time Warner Lambert invented atorvastatin, there were already four statins in the market. Nevertheless, the company decided to pursue atorvastatin in clinical trials and this ultimately led to the development of Lipitor® which is regarded as the most clinically superior drug in its class. It is particularly effective with respect to patients who have suffered a heart attack or suffer from acute coronary syndrome.¹⁶

Thirdly, research on chemical analogues leads to discovery of unexpected pharmacological properties. Apart from showing therapeutic superiority over the drugs of the same class, further research for chemical analogues can lead to discovery of unexpected pharmacological properties. For instance, imipramine, which was

¹² See Wertheimer, *supra* note 11 (providing several examples of drugs within the same therapeutic class that offer different efficacy profiles, different side effects and different drug – drug interaction, thereby, justifying their suitability for different sub – classes of patients); see also DIMASI & PAQUETTE, *supra* note 11 (arguing that “[C]linical responses to different drugs in a class can vary significantly by individual. Physicians traditionally have adopted a trial and error process for finding a drug in a class that works well for an individual patient.”); LAMATTINA, *supra* note 11; John Calfee, *Prices, markets, and the Pharmaceutical Revolution, Publication?*, (2000).

¹³ See C.A. Zarate et al., *Does intolerance or lack of response with fluoxetine predict the same will happen with sertraline?* 57 J. OF CLIN. PSYCHIATRY 67, 71 (1996).

¹⁴ See Wertheimer, *supra* note 11, at 100.

¹⁵ Joseph DiMasi, *Comment on “Me too drugs: Is there a problem?”*, available at <http://www.who.int/intellectualproperty/forum/HollisResponse.pdf> [“DIMASI”].

¹⁶ See DM Huse et al., *Cost-effectiveness of statins*, 82 (11) AM. J. OF CARDIOLOGY 1357, 1363 (1998).

being researched as an analogue to a neuroleptic, was found to have antidepressant properties,¹⁷ and gave the world one of its first antidepressants.

Further, innovation is incremental and cumulative. The proponents of “me-too” drugs argue that the critiques of “me-too” drugs misunderstand the nature of pharmaceutical innovation. Pharmaceutical innovation takes place in small doses and “me-too” drugs are important contributors to this progress, as it finally leads to optimal treatment options and discovery of new pharmacological properties.¹⁸

Me-too drugs do not represent imitation, but rather losers in the innovation race: The development of “me-too” drugs is not a product of imitation; rather it represents simultaneous development. Pharmaceutical firms often rely on the same basic research for screening drug candidates and often end up in an “innovation race” with different firms, simultaneously pursuing drugs with similar mechanisms of action.¹⁹ Thus, the first-in-class drug merely represents the winner of this race, whereas “me-too” drugs are the losers.

It is argued that attempts to regulate “me-too” drugs will have a chilling effect on pioneer drug research itself, since it will significantly increase the risk of failure i.e. the risk associated with coming second in the innovation race.²⁰

Lastly, “me-too” drugs offer price competition: Owing to the fact, that “me-too” drugs have similar therapeutic effects on patients, they compete with the first-in-class drug and thus, offer price competition that can substantially reduce drug prices.²¹

¹⁷ See Wermuth, *supra* note 10, at 128.

¹⁸ DiMASI & PAQUETTE, *supra* note 11, at 12; Wertheimer, *supra* note 11, at 86.

¹⁹ Joseph DiMasi & Laura Faden, *Competitiveness in follow-on drug R&D: A Race or Imitation?*, 10(1) NAT. REV. DRUG DISCOV. 23, 27 (2011) (finding that “Drug development can, therefore, often be characterized as a race in which several firms pursue investigational drugs with similar chemical structures or with the same mechanism of action, before any drug in the class obtains regulatory marketing approval.”); see also LAMATTINA, *supra* note 11, at 11.

²⁰ DiMASI & PAQUETTE, *supra* note 11, at 2, 3.

²¹ Thomas Lee, “Me-Too” Products — Friend or Foe?, 350 N ENGL J. MED 3, 4 (2004) [“Lee”]; DiMASI & PAQUETTE, *supra* note 11, at 12 (“Multiple drugs in a class also generate some degree of price competition. For example, DiMasi found that for every 20 new entrants that were introduced to the existing classes in the US from 1995 to 1999, 80% were launched at a discount to the price leader and 65% were launched at a discount to the average price for the class (actual transaction prices for a very large pharmacy-benefit manager were used).”).

B. *Arguments against the development of “me-too” drugs*

Pharmaceutical firms expend significant amount of money towards drug development and for conducting clinical trials,²² and this is often cited as the reason for the high prices of drugs. However, in the context of “me-too” drugs, critics argue that the insignificant additional therapeutic value of “me-too” drugs does not justify the costs of developing them and bringing them to the market.²³ The development of “me-too” drugs entails an opportunity cost: resources that could have been used to invent first-in-class drugs, for diseases that have few or no therapeutic options, and for high disease burdens,²⁴ are spent on developing “me-too” drugs for diseases for which therapeutic options already exist.²⁵

“Me-too” drugs compete with the first-in-class drugs in the marketplace thereby reducing the market share of the pioneer drug. This reduction in market share may reduce the ex-ante incentives to develop pioneer drugs, as the competitive returns for the pioneer drug may be insufficient to induce investment in research and development (R&D).²⁶

Critics of “me-too” drugs argue that costs of developing them are exacerbated, since they lead to “therapeutic class wars”. Pharmaceutical firms seek to attract consumer attention through aggressive marketing, conducting sponsored studies lacking scientific rigor and adopting switching campaigns to persuade patients to switch to “me-too” drugs by making misleading claims.²⁷ These practices not only lead to consumer deception, but also add to the wasteful expenditure incurred by pharmaceutical firms.

²² According to an oft-cited but highly disputed study, firms spend approximately US\$800 million (2000 dollars) for the development of a drug; see Joseph DiMasi et al., *The price of innovation: new estimates of drug development costs*, 22 J. OF HEALTH ECO. 151, 167 (2003).

²³ Joshua Gagne & Niteesh Chaudhary, *How Many “Me-Too” Drugs Is Too Many?*, 305 (7) JAMA 711 (2011) [“Gagne & Chaudhary”].

²⁴ Disease burden is the impact of a health problem. The World Health Organization measures burden of disease using the disability-adjusted-life-year (DALY). This time-based measure combines years of life lost due to premature mortality and years of life lost due to time lived in states of less than full health.

²⁵ Thomas Croghan & Patricia Pittman, *The Medicine Cabinet: What's In It, Why, And Can We Change The Contents?*, 23(1) HEALTH AFFAIRS 23, 24-25 (2004) [“Croghan & Pittman”].

²⁶ Frank Lichtenberg et al., *The Dual Effects of Intellectual Property Regulations: Within- and Between-Patent Competition in The US Pharmaceuticals Industry*, 45 J. OF L. & ECON. 643, 643 (2002) (finding that “between-patent competition affects innovative returns, particularly through creative destruction in the many high-tech industries”).

²⁷ David Kessler et al., *Therapeutic-Class Wars – Drug Promotion in a Competitive Marketplace* 331(20) N. ENGL J. MED 1350 (1994).

Furthermore, critics of “me-too” drugs offer the following responses to the arguments extended by the proponents of “me-too” drugs. It has been argued by the supporters of “me-too” drugs that their introduction in the market leads to price competition with pioneer drugs. However, studies have shown that “me-too” drugs do not compete with first-in-class drugs on price, at least till the introduction of the fourth drug²⁸ in the class.²⁹ A possible explanation for this is that as patients switch from the first-in-class drug to “me-too” drugs, the average “fit” between the drug attributes and consumer preferences improves and this allows pharmaceutical firms to maintain high prices. The increase in price may be due to a spatial effect: even though “me-too” drugs may not be superior to existing drugs, the fact that they are different in such dimensions as side – effect profile or convenience, make them more attractive and hence increasing their worth to patients.³⁰

Additionally, the pharmaceutical market does not function as a “true market”,³¹ since the demand for drugs is more inelastic and marketing campaigns by drug companies further skew the information asymmetries. Further, while it is expected of insurance companies to push back on payments for second-in-class drugs, unless they are cheaper than the first-in-class drugs, drug companies pay a significant amount of money to insurance companies seeking preferential listing of drugs.³² This also exposes the risks associated with relying on insurance companies to make an assessment of therapeutic benefits of drugs.

It has been argued that the development of “me-too” drugs provides various therapeutic alternatives. However, it is also a matter of concern that while “me-too” drugs increase therapeutic options, too many of such options can also lead to worse medical decisions.³³ Thus, unless “me-too” drugs are clinically superior, their introduction in the market may in fact, have adverse effects.

C. *Taking stock*

The above discussion suggests that the debate on “me-too” drugs is extraordinarily complex. This is substantiated by the fact that the current portfolio of drugs is skewed and the shortage of treatment options for emerging and neglected diseases

²⁸ Fourth drug in class refers to the fourth “me-too” drug bearing a similar chemical structure as the first in class drug.

²⁹ John Lu & William Comanor, *Strategic Pricing of New Pharmaceuticals*, 80 (1) REV. ECON. & STAT. 108 (1998); Joel Lexchin, *Do manufacturers of brand-name drugs engage in price competition? An analysis of introductory prices*, 174(8) CMAJ 1120, 1121 (2006).

³⁰ STUART SCHWEITZER, *PHARMACEUTICAL ECONOMICS AND POLICY* 147 (2nd ed., 2007).

³¹ LEE, *supra* note 21, at 4.

³² Gagne & Chaudhary, *supra* note 23, at 712.

³³ Gagne & Chaudhary, *supra* note 23, at 711; Donald Redelmeier & Eldar Shafir, *Medical Decision Making in Situations That Offer Multiple Alternatives*, 273(4) JAMA 302, 304.

contrasts with an apparent excess of treatment options for a few diseases.³⁴ Tuberculosis is an instructive example of this – a recent study found that no new chemical entity was approved (or was in clinical trials) for the treatment of tuberculosis during the years 2000 – 2011, even though it represents 5% of the Global Disease Burden in terms of Disability Adjusted Life Years (DALYs).³⁵ On the other hand, the proliferation of antidepressants (nine antidepressants have been approved from 1989 to 2004³⁶) is an appropriate example to illustrate the excessive investment in “me-too” drugs.³⁷ This suggests that a reform that realigns the incentives to develop drugs for a broader range of diseases is required. The opponents of “me-too” drugs would argue that this could be achieved by reducing pharmaceutical firms’ research in chemical analogues coupled with increased incentives to develop drugs for neglected diseases.³⁸ However, there are two underlying assumptions in this argument that need to be recognized.

The first assumption is that the preferred objective of drug research is to develop drugs for diseases with few or no therapeutic options as compared to developing drugs which provide more treatment options for a given indication. In the author’s opinion, at least from a societal perspective, this is a reasonable assumption considering the distributive effects of the former approach. At the same time, over-deterrence is a real concern here. First-in-class drugs may be far from the optimal treatment for a particular disease and thus reforms must be tailored such that the chilling effect on the development of “me-too” drugs is not excessive.

The second assumption is that the objective of reducing disease burdens for diseases with few or no therapeutic options is likely to be better served by research on developing a first-in-class drug as compared to researching on chemical analogues of known drugs. This second assumption is more controversial than the first. As noted, research on chemical analogues of known drugs has led to discovery of unexpected pharmacological properties. Thus, synthesizing chemical analogues may represent a legitimate strategy for firms to discover new pharmacological properties that help treat diseases having few therapeutic options. At the same time, it must be

³⁴ Croghan & Pittman, *supra* note 25, at 24-25 (“The shortage of drugs in development for chronic and emerging diseases contrasts with what appears to be excessive investment in new drugs in other areas, even when a disease represents a substantial social burden.”).

³⁵ Belen Pedrique et al., *The Drug And Vaccine Landscape For Neglected Diseases (2000–11): A Systematic Assessment*, 1(6) THE LANCET GLOBAL HEALTH e371, e379 (2013).

³⁶ Croghan & Pittman, *supra* note 25, at 24, 25.

³⁷ ANGELL, *supra* note 11.

³⁸ An initiative that has been particularly successful in promoting innovation for rare diseases is the Orphan Drugs Act, 1983 (passed in the US) that was designed to facilitate the development and commercialization of drugs to treat rare diseases. The Act, which is considered to be a success nearly universally, is a useful example of a successful attempt to realign incentives, leading to a broader portfolio of drugs.

borne in mind that further research on “me-too” drugs is undertaken on the basis of proven clinical effects and the discovery of unexpected properties can be merely “fortuitous”.³⁹ Thus, again, any reform targeting “me-too” drugs must be tailored such that it does not unduly chill legitimate and systematic attempts by pharmaceutical firms to pursue chemical analogues of known drugs for discovering new pharmacological properties, while at the same time giving greater impetus to the development of first-in-class drugs for diseases with few or no therapeutic options.

There is another important factor in the mix here. Second-in-class drugs or third-in-class drugs may sometimes be just losers in innovation races. These late entrants are a result of simultaneous development, and hence, any measures to regulate the development of “me-too” drugs must have regard for the consequent increase in the risk of losing the innovation race.

Thus, while there appears to be merit in the argument that the incentives for developing “me-too” drugs need to be restructured, the system needs to be designed carefully to ensure that legitimate and beneficial practices are not curtailed. Part IV shall examine the specific solutions that may help achieve this balance.

III. “FOLLOW – ON DRUGS”: PROBLEMATIC?

The development cycle of a drug often does not end with the marketing of the first drug containing a particular active ingredient. Pharmaceutical firms continue to modify existing products in the market, a process known as incremental innovation. Incremental innovation leads to the development of new forms of the drug such as a modification of the known active ingredient into another physical or chemical form and may even lead to discovery of new uses of the known drug.⁴⁰ In order to understand the niceties of this process, it is important to identify certain distinguishing features between “me-too” drugs and “follow-on” drugs: to begin with, “follow-on” drugs have the same or slightly modified active ingredient as the first-marketed drug (“first-generation product”), while “me-too” drugs only share the mechanism of action and the core structure with the first-in-class drug and thus, fall within the same therapeutic class.⁴¹ Secondly, “me-too” drugs are, in most cases, developed by brand-name pharmaceutical firms while “follow-on” drugs may be

³⁹ See Wermuth, *supra* note 11, at 128.

⁴⁰ It is important to point out that the discovery of new uses of known drugs is appropriately within the definition of “incremental innovation” but cannot be classified as a “follow on drug”.

⁴¹ *Supra* notes 1 and 2.

developed by the pharmaceutical firm that owns the patent for active ingredient (this is the most common case), by generic companies or by other brand name companies. This highlights another important distinction between the two: “me-too” drugs do not fall within the scope of the patent over the first-in-class drug while “follow-on” drugs are often covered within the scope of the patent over the first-generation product.

Akin to the debate on “me-too” drugs, there are arguments both in favour of and against the development of “follow-on” drugs. The next section provides an analysis of the same.

A. Arguments in favour of the development of “follow-on” drugs

Incremental innovation on a drug is often critical to realizing the full potential of the drug.⁴² It is well recognized that incremental innovation over first generation products has the potential to lead to drugs that provide significant gains in therapeutic effects. A typical example of Lamictal™, which is an anticonvulsant medicine for treatment of epilepsy, is cited in GlaxoSmithKline’s (“GSK”) Public Policy on Evergreening. Lamictal™ was initially marketed in the oral tablet form that was to be swallowed with a little water. The patent for the active ingredient of Lamictal™ was applied for in 1980 and the patent term expired in 2000 in many countries (such patents on the active ingredients of first-generation drugs are often referred to as “basic patents”). In 1992, GSK invented a chewable/dispersible tablet formulation of the active ingredient and this provided significant benefits in terms of ease of use and thus increased patient compliance. The formulation was separately patented and the patent ran till 2012 (such patents on new forms, uses or formulations are often referred to as “secondary patents”). In the meantime, after the expiry of GSK’s patent over the active ingredient in 2000, generic companies introduced their versions of Lamictal™, though they could not introduce such chewable/dispersible tablet formulation until after the expiry of the secondary patent. Thus, while the public was able to obtain generic versions of Lamictal™ after the initial term of 20 years of patent protection, pharmaceutical companies still had the incentive to develop versions of the drug that had increased patient compliance thus helping reduce the disease burden.

Brand-name pharmaceutical firms claim that the process of developing new forms, formulations or discovering new uses involves significant expenditure of R&D resources and thus merit separate patent protection. Much of the debate on drug

⁴² *GlaxoSmithKline’s Position on Evergreening*, GLOBAL PUBLIC POLICY ISSUES, GlaxoSmithKline Government Affairs, Public Policy and Patient Advocacy, available at <http://www.gsk.com/content/dam/gsk/globals/documents/pdf/GSK-and-evergreening.pdf>.

patenting revolves around the accessibility and affordability of medicines and the ease with which generics can enter the market. Proponents of the “follow-on” drugs are of the opinion, that since generics are free to enter the market with versions of the first generation product after the expiry of the patent thereon, the use of second-generation drugs is purely a matter of consumer choice and the more price-sensitive patients can choose to use the generic (typically cheaper) drugs.⁴³ It is further argued that unless the “follow-on” drug offered therapeutic benefits over the first-generation drug, patients and doctors could not have been convinced to use them.⁴⁴

B. Arguments against the development of “follow-on” drugs

The opponents of “follow-on” drugs respond to the argument that generics are free to launch the first-generation products after the expiry of the basic patent, by pointing out the practices adopted by brand-name companies pursuant to the development of second-generation products in order to extend the length of their exclusivity in the market.

Brand-name companies continue to modify first-generation products and often patent any improvements invented during the lifecycle of the first-generation products. Studies have revealed that this activity re-intensifies near the end of the patent term of the first-generation product. On an average, 2.97 patents cover one drug while drugs that received priority approval (and thus were probably more commercially important) are covered by 3.41 patents.⁴⁵

Such secondary patents help to bolster the exclusivity during the term of the basic patent and thereafter, extend the exclusivity enjoyed by the brand-name company.⁴⁶ This is done through a combination of strategies aimed at persuading patients to switch to second-generation products. These strategies, referred to as “bridging strategies”, include (i) launch of second-generation products close to the loss of exclusivity of the first-generation product; (ii) aggressive marketing aimed at

⁴³ Albert Wertheimer & Thomas Santella, *Pharmacoevolution: The Advantages Of Incremental Innovation*, IPN Working Papers On Intellectual Property, Innovation And Health <http://www.who.int/intellectualproperty/submissions/Pharmacoevolution.pdf>; Jonathan Darrow, *Debunking the Evergreening Patents Myth*, 131(6) HARV. L. RECORD 6 (2010).

⁴⁴ See *Final Report on the Pharmaceutical Sector Inquiry*, EUROPEAN COMMISSION (July 8, 2009) http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/staff_working_paper_part1.pdf.

⁴⁵ Lisa Ouellette, *How Many Patents Does It Take To Make a Drug? Follow-On Pharmaceutical Patents and University Licensing*, 17 MICH. TELECOMM. & TECH. L. REV. 299 (2010); Amy Kapczynski et al., *Polymorphs and Prodrugs and Salts (Oh My!): An Empirical Analysis of “Secondary” Pharmaceutical Patents*, 7(12) PLOS ONE e49470(2012) [“Kapczynski”].

⁴⁶ Scott Hemphill & Bhaven Sampat, *Evergreening, Patent Challenges, and Effective Market Life in Pharmaceuticals*, 31 J. HEALTH ECON. 327, 337 (2012); Kapczynski, *supra* note 45.

convincing doctors and patients to switch to the second-generation product emphasizing on the advantages of the second-generation over the first-generation product; (iii) use of instruments to delay entry of generics before the launch of the second-generation products including withdrawal of marketing authorizations for first-generation products,⁴⁷ intervening in the marketing approval process for the generic product, intervening before the reimbursement bodies as regards pricing of generic drugs or expressing concerns about generic versions of their products and (iv) Withdrawal of first-generation product before generic entry, which forces doctors and patients to switch to second-generation products (such withdrawals are usually carried out shortly after the launch of the second-generation products and before loss of exclusivity of the first-generation product).

The cumulative effect of these strategies is that entry of generic versions in the market is delayed and patients often switch to typically more expensive second-generation products even though such products offer trivial advantages over the first-generation products. This problem is further exacerbated by the information asymmetry prevalent in this industry and the close association between doctors and pharmaceutical companies.

Further, opponents of “follow-on” drugs argue that incremental innovation offers little therapeutic benefit to patients especially considering the significant amount of funds that are utilized for their development and promotion.⁴⁸

C. Concerns raised by “follow-on” drugs

The primary concern presented by “follow-on” drug development, as mentioned above, is the potential delay that it may cause in the entry of cheaper generic versions in the market and the switching of patients to second-generation drugs, even though they do not offer sufficient therapeutic benefits commensurate with their cost. It may be argued that generic companies can launch similar campaigns to inform patients regarding the lack of therapeutic advantages of the second-generation drugs; however, it is unclear if this is feasible considering the relative financial strength of generic companies. In any event, such marketing campaigns will entail significant costs that will escalate the costs of the generic versions of the drug. The net result would be delay or denial of access to affordable medicines.

⁴⁷ See the decision of the European Court of Justice in Case C-457/10 P, AstraZeneca plc v. Eur.Comm’n, [2012] (ECJ), 6 December 2012), holding that AstraZeneca abused its dominant position on the market by misleading patent authorities and misusing the regulatory system in order to prevent generic competition against its anti-ulcer medicine.

⁴⁸ Donald Light & Joel Lexchin, *Pharmaceutical research and development: what do we get for all that money?*, 345 BRIT. MED. J. e4348 (2012).

Further, the expenditure incurred in the development and promotion of second-generation drug, that offer trivial benefits, reduces the R&D expenditure available for the development of pioneer drugs that are capable of reducing disease burdens for diseases which have few or no treatment options.

At the same time, as with “me-too” drugs, it is important to recognize that follow-on drugs can provide significant benefits over the first-in-class drugs and may help in satisfying unmet needs.⁴⁹ Thus, a balanced approach must be employed again, such that the incentives for pharmaceutical firms to develop “follow-on” drugs are not unduly reduced.

In addition to this, there is also a need for incentivizing discovery of new uses of known drugs. It is often contended by pharmaceutical firms that breakthrough innovation is becoming increasingly difficult since all the “low hanging fruit has been plucked”.⁵⁰ At the same time, it is also well recognized that drugs can have a diverse range of therapeutic effects on humans. An oft-quoted example in this context is sildanefil citrate (sold by Pfizer under the brand name Viagra®). The drug was first developed for treatment of pulmonary hypertension and angina and it was only during Phase I trials of the drug that its effects with respect to erectile dysfunction were observed.⁵¹ Considering the high rate of failure of new chemical entities in clinical trials,⁵² discovery of new uses of known drug is turning out to be the most effective way to move from target identification to the clinic.⁵³

D. Are the problems related?

It is possible that the issues of excessive R&D expenditure in “me-too” drugs and “follow-on” drugs are interrelated. As noted above, “me-too” drugs have the potential of significantly reducing the market share of the first-in-class drug, thereby leading to competitive returns. This may reduce incentives for pharmaceutical firms to invest in development of pioneer drugs and they may be encouraged to pursue incremental innovation to extend their exclusivity over drugs that have been successful in the market and have provided an assured revenue stream. Consider a scenario in which a manager of a large pharmaceutical firm has two drug candidates out of which he has to approve one for further research. One drug candidate is a “follow-on” drug for a patented blockbuster drug and the other has the potential of

⁴⁹ See *id.* § III.A.

⁵⁰ FREDRICK ABBOTT ET AL., *GLOBAL PHARMACEUTICAL POLICY: ENSURING MEDICINES FOR TOMORROW'S WORLD* (2nd ed., 2011).

⁵¹ LAMATTINA, *supra* note 11, at 17.

⁵² Joseph DiMasi et al., *Trends in Risks associated With New Drug Development: Success Rates for Investigational Drugs*, 87(3) *CLIN. PHARMACO. & THER.* 272, 276 (2010).

⁵³ S Dakshanamurthy et al., *Predicting new indications for approved drugs using a proteochemometric method*, 55(15) *J. MED. CHEM.* 6832, 6848 (2012).

a being a pioneer drug. The higher risk of failed clinical trials and rejection by the market already weigh in favour of pursuing the “follow-on” drug. Another factor that may weigh against the pioneer drug is that development of a pioneer drug is likely to induce other pharmaceutical firms to develop “me-too” drugs thereof and this may reduce the market share of first-in-class drug. Thus, the possibility of “me-too” drugs being developed may incentivize the development of “follow-on” drugs. While this hypothesis needs to be validated through empirical data and analysis, it may merit further consideration.

IV. SOLUTIONS

In this Part, the author suggests broad solutions which can be incorporated into a model in order to restructure incentives for pharmaceutical innovation and for achieving optimal allocation of resources expended for pharmaceutical innovation. The solutions mentioned in this part are generalized and are not directed towards incorporation into a particular model.

A. Using comparative benefit – risk profiles

Experience has shown that a “me-too” drug or a “follow-on” drug can exhibit significantly higher efficacy as compared to the first-in-class drug or the first-generation drug respectively and this may be particularly true for certain sub-classes of patients. Any restructuring of the system of incentivizing drug development must reduce incentives for development of drugs which show no or trivial change to benefit – risk profile of existing drugs. The reward/incentive associated with developing a “me-too” drug must be commensurate with its benefit – risk profile, as compared to the best drug in the therapeutic class i.e. the drug demonstrating the most optimal benefit – risk profile within the therapeutic class. Similar comparative analysis can also be carried out for second-generation drugs with respect to the first-generation drug. If the potential reward at the end of the research is reduced, the risks of undertaking the research will increase significantly, thereby reducing the ex-ante incentives for pharmaceutical firms to undertake projects pertaining to “me-too” drugs and “follow-on” drugs. At the same time, the drugs that do exhibit enhanced benefit – risk profiles should be adequately incentivized.

The author further suggests that this comparative analysis should be conducted on the basis of clinical benefits and risks of the drug under consideration as opposed to the efficacy of a drug observed *in vitro* or *in vivo*. Scholars, like Guo, have reviewed the wide array of methodologies that have been developed in the field for assessing

risks and benefits of a drug.⁵⁴ A few promising ones which may be appropriate for conducting a comparative analysis are Qualitative Framework for Risk and Benefit Assessment, Quality Adjusted Time without symptoms and toxicity, Incremental Net Health benefit (QALYs) and Multicriteria Decision Analysis. The comparative analysis of the effectiveness of drugs is an emerging science and is being undertaken both at the public and the private level. For instance, the Drug Effectiveness Review Project, started in the year 2003, is a collaboration of public entities that have joined together “to produce systematic, evidence-based products of the comparative effectiveness and safety of drugs in many widely used drug classes, and to apply the findings to inform public policy and related activities in local settings”.⁵⁵

B. Simultaneous development of “me – too” drugs: The Innovation Race Problem

As noted in the context of “me-too” drugs, the first-in-class drug is often merely the winner in the innovation race and later entrants in the same class may be the result of simultaneous development by different pharmaceutical firms. In order to mitigate the risk of failure for pharmaceutical firms entering this race, the author suggests that the system should allow pharmaceutical firms to adduce proof of conception of their drug. If a pharmaceutical firm provides sufficient evidence that it had been developing the “me-too” drug prior to first public disclosure of the first-in-class drug, it should be entitled to the reward/incentive. However, there is a danger lurking in this suggestion – if identical rewards are given to the first-in-class manufacturer and a later entrant, it is possible that it will slow down the innovation race as a whole. Thus, in order to incentivize pharmaceutical firms to win the innovation race, drug regulators may consider granting expedited reviews to pharmaceutical firms that submit an application for approval of first-in-class drugs.⁵⁶

⁵⁴ Jeff Guo et al., *A Review of Quantitative Risk–Benefit Methodologies for Assessing Drug Safety and Efficacy—Report of the ISPOR Risk–Benefit Management Working Group*, 13(5) VALUE HEALTH 657, 660 (2010).

⁵⁵ *Drug Effectiveness Review Project*, CENTRE FOR EVIDENCE BASED POLICY, OREGON HEALTH & SCIENCE UNIVERSITY, <http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/index.cfm>.

⁵⁶ Such procedures have already been adopted by a few regulatory agencies around the world. For instance, the Food and Drug Administration in the United States has adopted three approaches (Priority Review, Accelerated Approval, and Fast Track) for expediting the review process of drugs which show clinical superiority over the drugs available in the market. *See*

<http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/speedingaccessstoimportantnewtherapies/ucm128291.htm>.

C. *Incentivizing new uses of known drugs*

As argued above, there are advantages to protection of new uses of known drugs. Developing countries have often denied new uses of known substances on the basis that the R&D resources required for discovery of such new uses are much lesser than the R&D resources needed for development of a new molecule and thus such discoveries do not require similar incentives, such as patent protection.⁵⁷ However, a strategy of total exclusion from patentability may have a chilling effect on a promising area for research and therefore a more balanced approach is called for. This could be in the *sui generis* forms of protection for new uses of known drugs. The suggestions by UNCTAD to developing countries in this context are promising. UNCTAD has suggested that countries could consider a *sui generis* mode of protection for new uses akin to a “utility model”,⁵⁸ or a “compensatory liability regime” i.e. a “use and pay”⁵⁹ regime.⁶⁰

V. MODELS

As far as the pharmaceutical industry is concerned, the legal system and the models of incentives it creates often dictate the nature of drugs that are developed and marketed. The existing models of incentives can be broadly classified into three groups namely, (i) grant of patent protection; (ii) grant of regulatory approval and (iii) reimbursement of costs of the drug by governmental agencies and drug price regulation.⁶¹ For the purposes of this article, the author shall examine the first model in detail and briefly examine the feasibility of using other models for incorporating the solutions proposed above.

A. *Restructuring incentives through the patent model*

The grant or denial of patents has been one of the most influential mechanisms in tailoring the scope of drug discovery and research. It is well recognized that pharmaceutical firms are acutely conscious of the patentability of any drug candidate and drug candidates are often dropped even though they exhibit outstanding

⁵⁷ For instance, see § 3(d), The Patents Act, *supra* note 3.

⁵⁸ Utility model protection is similar to the protection under patent law but is usually for a shorter term. The requirements for obtaining utility model protection are also usually less stringent.

⁵⁹ Under the “use and pay” model, the right-holder is not be entitled to exclude others from entering the market but is entitled to royalty for the use of the invention.

⁶⁰ UNCTAD REFERENCE GUIDE, *supra* note 8.

⁶¹ These models are only representative of the current models that are employed for incentivizing drug development. Other models, such as the Orphan Drugs Act exist, and several models, such as a prize system for pharmaceuticals, have been proposed.

therapeutic potential in pre-clinical testing if they are believed to be ineligible for a patent.⁶²

In the context of regulating “follow-on” drugs and “me-too” drugs through denial of patents, we do not start on a clean slate. A few countries have already introduced patent reforms directed at modifying incentives for discovery of “follow-on” drugs. It will be appropriate to examine these reforms first.

1. The Indian model

Pursuant to the TRIPS, India amended its statute in the year 2005 ushering in a pharmaceutical product patent regime amidst intense debates in the Parliament regarding the anticipated rise in prices of pharmaceuticals following the amendments. In order to mitigate the anticipated rise in prices,⁶³ India introduced a unique provision in its patent law that has since gained prominence and is serving as a model for similar laws in other countries. Section 3(d) of the Patents Act, 2005 is worth extracting:

“3. The following are not inventions within the meaning of this Act,—

....

d) the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance....

Explanation - For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy.”

The interpretation of the term “efficacy” in Section 3(d) has been subject to significant amount of litigation. In a landmark decision delivered last spring,⁶⁴ the Supreme Court of India held that the term “efficacy” in Section 3(d) means “therapeutic efficacy” and this necessarily excludes properties that are inherent to the drug. In this case, grant of a patent was denied to Novartis’ drug GLEEVEC® that contains a polymorphic version of the active ingredient. The Supreme Court held that since the active ingredient, imatinib base, had been patented earlier and its efficacy was known, Novartis was not entitled to a patent on the polymorphic form

⁶² Benjamin Roin, *Unpatentable Drugs and the Standards of Patentability*, 87(3) TEX. L. REV. 503, 537-538 (2009) [“Roin”].

⁶³ See Debates before the Indian Parliament held on March 18 – 22, 2005 regarding the enactment of the Patents (Amendment) Act, 2005 [on file with author].

⁶⁴ Novartis AG v. Union of India & Ors., (2013) 6 SCC 1 (India) [“Novartis”].

of the imatinibmesylate (a salt), since it had failed to exhibit any enhancement of therapeutic efficacy.

While the Novartis decision clarifies that Section 3(d) is applicable to “follow-on” drugs, the scope of the provision as regards “me-too” drugs remains unclear. As the provision is directed towards new forms of known substances that include ‘derivatives of known substance’, a few generic manufacturers have attempted to argue that chemical analogues of known substances should also fall in this category. However, we are yet to receive judicial interpretation on this issue.

Section 3(d) has served as a model for countries like Philippines⁶⁵ and Argentina⁶⁶ that have introduced nearly identical provisions to deny patentability to new forms of known substances. It is noteworthy that under the guidelines for examination of patents in Argentina, the bar to patentability of new forms is absolute and patentees cannot seek a patent even where the new form of the known substance demonstrates enhanced efficacy.

2. The Non – obviousness model

The patentability of “me-too” drugs has also been called into question for their failure to satisfy the inventive step requirement. Under the law prevalent in the United States, if structural similarities between the known drug and the “me-too” drug create a reasonable expectation that the “me-too” drug will possess similar properties, then a *prima facie* case of obviousness is established and this may be rebutted through proof of unexpected and surprising properties.⁶⁷

3. Drawbacks of the ‘patents approach’

Insufficient information: Patent applications are filed at an early stage in the development process of a drug when only preclinical data is available.⁶⁸ Thus, patentability decisions are often made based on preclinical information such as *in vitro* and *in vivo* results that are an imperfect proxy for the effects seen in human

⁶⁵ See PHILIPPINES INTELLECTUAL PROPERTY CODE, § 22, *supra* note 4.

⁶⁶ *Guidelines for Patentability Examination of Patent Applications Directed to Chemical and Pharmaceutical Inventions*, *supra* note 5.

⁶⁷ *Roin*, *supra* note 62, at 538; *Imperial Chem. Industries, PLC v. Danbury Pharmacal, Inc.*, 777 F. Supp. 330, 373 (D. Del. 1991) (The Court held the patent on atenolol invalid for being obvious, because of “atenolol’s lack of unexpected properties and advantages over the prior art beta-blockers”).

⁶⁸ BRUNO GALLI & BERNARD FALLER, *Discover a Drug Substance, Formulate and Develop It to a Product*, THE PRACTICE OF MEDICINAL CHEMISTRY 858 (Wermuth ed., 3rd ed., 2011) [“The correct time to file a patent is a subtle balance between too early (the patent protection clock already starts) and too late (competition). It is at this (lead optimization) stage that one usually applies”].

population.⁶⁹ The GLEEVEC® example in this regard is instructive. The Indian Supreme Court had denied the grant of a patent to the polymorphic form of imatinibmesylate on the basis that it did not demonstrate enhancement of known efficacy of imatinib. However, the comparison carried out by the Supreme Court was on the basis of pre-clinical data.⁷⁰ The “known substance” on the basis of which GLEEVEC® was denied a patent never reached clinical trials since it could not be administered to humans.⁷¹ Thus, despite being the first drug in its therapeutic class that reached the market, GLEEVEC® was denied patent due to the focus of patent law on disclosures made in previous literature. In a nutshell, patent law has traditionally assessed patent applications based on the disclosures made at the time of filing of the patent application rather than the real world effect of the commercialized products,⁷² and thus it is not an appropriate model for applying a comparative efficacy standard.

Patent law is an inappropriate model for the solution: As noted above, owing to the heterogeneity of the human population, “me-too” drugs and “follow-on” drugs may satisfy unmet needs of a sub-class of the patient population. In order to strike an appropriate balance between maintaining incentives for the inventor of the first-in-class drug and ensuring adequate levels of beneficial incremental innovation, the system needs to be tailored to make the reward for “me-too” drugs or “follow-on” drugs commensurate with the benefits to the particular sub-class of patients. Thus, the model needs to be designed in a manner, such that, it can regulate the indication or the sub-class of patients for which the drug is sold in the market. However, denial of patent protection is an imperfect and inefficient approach to regulate the manner in which drugs are sold in the market.

In the author’s opinion, authorities examining patents have inadequate expertise to make determinations of risks and benefits of drugs. Pharmaceutical patents are traditionally examined by chemists rather than pharmacologists and thus, they lack the specialized skill set required for making complex assessment of benefits and risks associated with drugs. Even specialized bodies such as drug regulatory authorities, that are better equipped to make such decisions, often make mistakes regarding the safety and efficacy of the drug. In these circumstances, it will be unfair to expect that patent examiners, who lack expertise in the subject, will fare better in making such decisions. In recognition of this issue, the law in the Philippines entitles a patent examiner to call on the representatives of the Bureau of Food and Drugs and/or its delegated experts to provide an expert opinion with regard to significant enhancement of therapeutic efficacy.

⁶⁹ *Id.*

⁷⁰ NOVARTIS, *supra* note 64, at 92.

⁷¹ NOVARTIS, *supra* note 64, at 182, 153.

⁷² Roin, *supra* note 62, at 536 – 538.

Further, pharmaceutical firms – both brand-name and generic – often file defensive patents,⁷³ and the number of patent applications filed far exceeds the number of drugs that are introduced in the market. Thus, conducting costly efficacy analysis, while determining patentability of such patents, is a wasteful and inefficient process.

Denial of patent only reduces ex-ante incentives to develop “me-too” drugs: While denial of patent protections reduces ex-ante incentives for development of “me-too” drugs, if a drug is developed and found not to demonstrate a superior benefit-risk profile, pharmaceutical firms may still undertake marketing strategies to promote its drug and compete with the first-in-class drug. The patent is only one form of exclusivity enjoyed by a drug and it is probable that even though such drugs may be denied a patent, they may still be able to stave off generic competition based on data exclusivity provisions available under drug regulatory laws.⁷⁴ Since the introduction of drugs that do not exhibit better benefit–risk profiles is likely to lead to worse medical decisions and expose consumers to post-approval adverse reactions, such drugs are likely to have an adverse impact on consumer welfare.

Hurdles caused by harmonization: Patent law has been harmonized across the world through TRIPS and various bilateral and multilateral Free Trade Agreements, and many such agreements are in the pipeline. These Agreements severely restrict the ability of nations to reform their patent laws. For instance, it appears that Section 3(d) of the Indian Patent Act may violate the non-discrimination clause of the TRIPS, since the Indian Supreme Court has held that the provision sets higher standards of patentability for pharmaceuticals and represents a “second tier of qualifying standards”, apart from the requirements of novelty, inventive step and utility.⁷⁵ Further, in view of the recent developments with respect to the Trans Pacific Partnership Agreement through which the United States endeavours to thwart attempts by other countries to deny patents to “me-too” drugs or “follow-on” drugs, it is unlikely that countries will be able to reach a consensus on this issue. A possible solution to this issue may be to ratchet up the inventive step requirement since the TRIPS does not define a particular standard of inventive step and thus, provides member countries greater flexibility in applying a higher standard of inventive step.

⁷³ For example, pharmaceutical firms, both generic and brand – name, have filed over 15 patents covering different crystalline forms of imatinibmesylate. However, all pharmaceutical firms currently sell the beta crystalline form of imatinibmesylate. *See* Documents handed over by Novartis AG during oral hearing of NOVARTIS [on file with author].

⁷⁴ *See* Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 505(c)(3)(E) & § 505(j)(5)(F) (1938), which provides for data exclusivity of new drug products under the mentioned sections.

⁷⁵ NOVARTIS, *supra* note 64, at 57.

Considering the significant drawbacks outlined above, the patent model may not be an appropriate model for incentivising the development of “me-too” drugs and “follow-on” drugs.

B. Other models

Modifying the criteria for obtaining regulatory approvals: Angell and Relman have suggested that “me-too” drugs should be denied regulatory marketing approval unless they show “greater clinical effectiveness, greater safety, fewer side effects or substantially greater convenience” as compared to the existing drug.⁷⁶ Other scholars who have written on this issue have also supported this proposal.⁷⁷

This model does not have most of the drawbacks of the patent model identified above. However, there is an over-deterrence concern that exists. The possibility of denial of marketing approval significantly increases the risk of failure for pharmaceutical firms. Increased risk-taking costs may have the disastrous consequence of increasing the prices of drugs across the board.

It is also well recognized that the grant of regulatory approval is usually not conclusive of the efficacy and safety of the drug, especially owing to the smaller sample size of clinical trials. Drugs that have been approved by the regulatory authorities have often revealed adverse reactions during post marketing surveillance.⁷⁸ In these circumstances, it would be critical to have a second-in-class drug as a fall-back option which the doctors and patients could switch to, should the first-in-class drug fail after launch in the market.

Further, third party intervention to challenge the efficacy and safety claims of pharmaceutical firms will be difficult since the data generated for clinical trials is protected by data protection laws.

However, this does not mean that this model is entirely without merit. It is the opinion of the author that with a little modification, this model may be effective. For instance, rather than taking the harsh step of denying marketing approval, regulatory bodies can tune down the number of years of data exclusivity based on the benefit-risk profile demonstrated by the “me-too” drug. Simultaneously, the inventive step requirement of patent law can be amended such that a patent on a “me-too” drug can be denied or revoked, unless the “me-too” drug demonstrates a

⁷⁶ RELMAN & ANGELL, *supra* note 11; ANGELL, *supra* note 11.

⁷⁷ Hollis, *supra* note 11.

⁷⁸ See, e.g., Timothy Brewer & Graham Colditz, *Post Marketing Surveillance and Adverse Drug Reactions: Current Perspectives and Future Needs*, 281(9) JAMA 824-829 (1999).

significantly enhanced benefit-risk profile, as determined by the drug regulatory body.

The reimbursement of costs model and the price regulation model: Under the reimbursement of costs model, the governmental agency may refuse to reimburse costs of “me-too” or “follow-on” drugs that do not exhibit significantly better benefit-risk profiles than known drugs. Similarly, under the price regulation model, national governments regulate the price of “me-too” drugs and “follow-on” drugs and ensure that the price gap between the known drug and the new entrant (whether “me-too” or “follow-on”) is commensurate with the medical benefit provided by such drugs.

These models appear to be quite promising. They do not restrict the entry of the “me-too” drug into the market and thus avoid the over-deterrence effect associated with the denial of marketing approval. Further, the determination of the cost-effectiveness of a drug by an independent governmental agency provides reliable information to consumers, thereby curing the information asymmetry and allowing them to make an informed choice. It is also noteworthy that such models not only compare the benefits and risks of the drugs but also add the cost component that can be critical from the standpoint of the consumer. However, there is one drawback to the price regulation system – the ‘forceful’ lowering of prices of the “me-too” drug may in fact be detrimental to the interests of the manufacturer of the best-in-class drug, since it is possible that patients may choose to consume the “me-too” drug, thereby reducing the market share of the best-in-class drug.

Models of this kind are already being implemented in countries such as the United Kingdom and Germany. In the United Kingdom, the National Institute for Health and Care Excellence measures the cost-effectiveness of a treatment on the basis of Quality Adjusted Life Years (QALYs) and refuses to reimburse costs of the drug that do not show an enhancement of QALYs.⁷⁹ Similarly, Germany uses an “early benefit assessment” for regulating the price of the “me-too” drugs. The new drug is compared with the “appropriate comparator therapy” and depending on whether the drug has an additional benefit or not, the price is negotiated between the manufacturer and the German National Association of Statutory Health Insurance Funds or defined directly.⁸⁰ France adopts a dual system combining both the reimbursement of costs model and the price regulation system. The governmental agency carries out Medical Benefit Assessments (SMR) under which drugs are given

⁷⁹ See *Measuring Effectiveness and Cost Effectiveness: the QALY*, National Institute for Health Care and Excellence, <http://www.nice.org.uk/newsroom/features/measuringeffectivenessandcosteffectivenessstheqaly.jsp>.

⁸⁰ See SOZIALGESETZBUCH V[SGB V][SOCIAL CODE], § 35(a) (Ger.).

the level of ‘major’, ‘important’, ‘moderate’, ‘weak’, ‘insufficient to justify a reimbursement’ on the basis of the drug’s efficacy and safety, position of the medicine in the therapeutic strategy and the existence or absence of therapeutic alternatives, severity of the disease, type of treatment (preventive, curative or symptomatic) and the public health impact. This process is to appraise whether drugs merit reimbursement. The agency further carries out the Improvement of Medical Benefit Assessment (ASMR) based on the benefits provided by the drug as compared to existing drugs or therapies. The ASMR grading provides a basis for price fixing in comparison with alternatives. “Me-too” drugs and “follow-on” drugs which do not demonstrate improvement in medical benefits are given the lowest ASMR rating and may not be reimbursed or may be priced lower than the known drug or both.⁸¹

One significant drawback of the reimbursement of costs model is that its practical implementation is likely to be limited to developed countries, since governments in developing countries have insufficient infrastructure and funds for such government-funded reimbursement of costs schemes. However, this drawback is not present in the price regulation model and appears to be an attractive proposal for developing countries.

VI. CONCLUSION

The debate regarding “me-too” drugs and “follow-on” drugs is a complex one and countries would be ill-advised to adopt sweeping legislation or policies without balancing the over-deterrence and under-deterrence concerns. Countries must thus make informed policy choices and any reform should attempt to balance need for maintaining adequate incentives for pioneering innovation with the need for ensuring sufficient levels of beneficial incremental innovation.

This note makes three proposals for achieving this balance:

(i) Use of comparative benefit-risk profiles for determining the benefits and risks of “me-too” drugs as compared to the “best-in-class drug”: The reward or incentive provided to the late entrant must be commensurate with the comparative benefit-risk profile it demonstrates as compared to the best drug in the class. A similar comparative analysis can also be carried out for second-generation products with respect to first generation products.

⁸¹ Nathalie Grandfils, *Drug price setting and regulation in France*, (Inst. for Res.& Doc. in Health Econ., Working Paper, Sept. 2008), available at <http://www.irdes.fr/EspaceAnglais/Publications/WorkingPapers/DT16DrugPriceSettingRegulationFrance.pdf>.

(ii) In order to solve the innovation race problem, it is suggested that pharmaceutical firms must be allowed to adduce proof that their drug was already in development before the first public disclosure of the first-in-class drug. In order to avoid a slowing down of the race, the winner could be exclusively granted an accelerated review by the regulatory authorities.

(iii) Countries may also adopt *sui generis* protection for incentivizing the discovery of new uses of known drugs. This could be similar to a utility model or a compensatory liability model.

In the view of the author, the patent system is not the appropriate model for restructuring the incentives in pharmaceutical innovation. The drug regulatory model is promising though it raises over-deterrence concerns. A more balanced approach for realigning the incentives would be to make the term of data exclusivity commensurate with the additional benefits demonstrated by the concerned drug as compared to the known drug. Finally, the price regulation model appears to be a promising model for developing countries that may prove a viable alternative for incorporating the solutions identified above.