



The Value Of Incremental Pharmaceutical Innovation: Benefits For Indian Patients and Indian Business

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INTRODUCTION

India is fast emerging as a major global hub of innovation. Since it embarked on a period of economic liberalization in 1991, India has experienced dramatic growth in gross domestic product (“GDP”), achieving annual GDP growth rates as high as 9.6% by 2006-7.¹ This sustained economic growth has been due in part to a substantial increase in domestic investment in research and development (“R&D”), which grew seven-fold between 1991 and 2004² and led to pronounced innovative activity across a broad range of fields, including biotechnology, pharmaceuticals, automotive parts and assembly, aerospace technology, information technology and software. The result has been the development of new, high-quality products and services and the tapping of new markets through innovative, low-cost delivery mechanisms. India’s exports have, moreover, risen steadily since 1991, reaching an annual growth rate of 16% by 2007, indicating that Indian companies are competing successfully on the global stage, aided by such advances in innovation.³ By fueling India’s massive economic growth, innovation has contributed to the expansion of India’s middle class and declining poverty levels, and has thus been a key driver of India’s recent social and economic transformation.

Recent changes in India’s pharmaceutical sector have been emblematic of India’s transition from an “imitator” to an “innovator” nation. Until the 1990s, the domestic Indian pharmaceutical industry was characterized by a strong generic sector, but little investment in new drug development. R&D investment by Indian pharmaceutical companies was correspondingly very low, and typically focused on reverse engineering and novel process development. Beginning in the early 1990s, however, pharmaceutical R&D as a percentage of sales jumped from 0.4% to as much

as 4.8% by 2004. By 2006, India’s three largest pharmaceutical firms—Dr. Reddy’s, Sun Pharmaceuticals, and Ranbaxy—were investing approximately 12 – 18% of their annual sales revenue in R&D, a level comparable to leading global innovator firms such as Pfizer and GlaxoSmithKline.⁵ To protect their innovations, Indian pharmaceutical firms began filing an increasing number of patent applications in India and abroad directed at new drug discoveries,⁶ new drug delivery systems, and novel manufacturing processes, among other innovations. An important impetus for this increase in innovative pharmaceutical activity was provided by the amendment of India’s patent law in 2005 to permit the patenting of pharmaceutical products, which since 1970 had been protected only through method or process patents. This paradigm-shift in India’s intellectual property policy provided a crucial incentive for Indian companies to engage in new drug R&D and reinforced the emergence of a vibrant and dynamic research-based sector within the domestic pharmaceutical industry.

A substantial bottleneck to India becoming a major source of global innovation, however, remains its policy towards *incremental pharmaceutical innovation*. Among other things, incremental pharmaceutical innovations involve the discovery of new forms and uses of existing chemical compounds or substances, which lead to the development of safer, more efficacious and more useful drugs that are better-suited to particular patient profiles or needs and result in improved patient compliance and greater overall well-being.⁷ Incremental pharmaceutical innovations also provide the basis for the discovery of breakthrough drugs, as thousands of smaller incremental innovations lay the foundation upon which “blockbuster” drugs are discovered.⁸ In addition, in recent years, incremental pharmaceutical innovations have accounted for as much as 65% of new drug approvals by regulatory

agencies and roughly US\$17 billion of new retail prescription drug spending between 1995 and 2000 in the US alone. Incremental pharmaceutical innovations thus represent substantial annual revenue for pharmaceutical firms and an important return on R&D investment.⁹

Notwithstanding the demonstrable value of incremental pharmaceutical innovation, India’s present patent law does not promote or protect such innovation. Under Section 3(d) of India’s Patents Act, incremental pharmaceutical innovations—including new forms of known pharmaceutical substances—are not patentable unless they result in significantly enhanced “efficacy” of the active substance. By limiting in this manner the eligibility of incremental pharmaceutical innovations for patenting, Section 3(d) discourages R&D into such innovations, including new routes of administration, new dosage forms, and other innovations that would result in the development of drug products that are well-suited to the needs of Indian patients. Moreover, Section 3(d) acts as a disincentive for Indian pharmaceutical companies who might otherwise capitalize on the economic opportunities presented by incremental pharmaceutical innovations in India and abroad. Section 3(d) also discourages foreign direct investment into India that would substantially benefit the Indian economy. Indeed, *despite the increasing harmonization of intellectual property norms, India stood alone as the only country in the world to exclude the full range of incremental pharmaceutical innovations from patent eligibility when it adopted Section 3(d) in 2005.*¹⁰

The chief rationale for Section 3(d) is the concern that patent protection for incremental pharmaceutical innovations will encourage patent “evergreening,” or, the attempt to circumvent patent expiration on a drug product by seeking additional patent coverage for modifications of the product. Supporters of Section 3(d) argue that patent evergreening prevents inexpensive

In 2005, India stood alone as the only country to exclude the full range of incremental pharmaceutical innovations from patent protection.

generic versions of a patented product from entering the market, which in turn keeps drug prices elevated and reduces access to medicine by Indian patients. As discussed below, however, concerns regarding patent evergreening are more effectively addressed through rigorous application of the existing patentability requirements in Indian law—i.e., the requirements of *novelty*, *inventive step*, and *industrial application*—than through the wholesale exclusion of an entire category of pharmaceutical inventions from patent eligibility. Moreover, contrary to the prevailing view, a patent system that creates incentives for incremental innovation can in fact lead to decreases in costs and increased access to medicines by, for example, reducing overall treatment costs, reducing hospitalization and worker absenteeism, and reducing drug prices due to increased price competition. Such a system can, therefore, improve overall quality of life in India. By encouraging investment into domestic pharmaceutical research and skill development, such a system can also play an important role in fostering India's emergence as a major pharmaceutical producer and the transformation of Indian companies into major powerhouses in the global pharmaceutical industry.

In what follows, we outline these and other benefits of incremental pharmaceutical innovation to Indian patients and Indian businesses and suggest reform of Indian's patent law to enable Indian patients and Indian pharmaceutical companies to realize the full extent of these benefits. Among other sources, we draw upon studies of the impact of incremental pharmaceutical innovations on the economies of developed and developing nations as well as current case law in India regarding the

scope and application of Section 3(d). In addition, our analysis reflects the results of interviews of key stakeholders directly or indirectly associated with the Indian pharmaceutical sector, including policy formulators; academics and researchers; NGOs, pressure groups and civil society groups; Indian pharmaceutical companies; and subject-matter experts such as patent attorneys, scientists, and journalists.

I. THE NATURE OF INCREMENTAL PHARMACEUTICAL INNOVATION

A. Radical vs. Incremental Innovation in the Pharmaceutical Industry

Innovation—the development of new ideas, methods, or products—is commonly divided into “radical” and “incremental” variants. A radical innovation may be understood as a new product, process or system that results from a technological breakthrough, or the application of a technology having a far-reaching impact. The advent of the cellular telephone is a recent example of a radical innovation. Incremental innovation, on the other hand, involves technical modifications of an existing product, process or system that results in some improvement or enhancement thereto. The development of cell phones that are capable of taking photographs is thus an example of an incremental innovation, which resulted from the incremental combination and modification of existing technology in two previously discrete industrial fields.

Despite the tendency to think of radical and incremental innovation as two fundamentally different types of innovation, it is important to recognize that they are often interrelated and depend on one other. Radical innovations often result from many, smaller improvements carried out by different individuals and organizations over time. For instance, electric light—a paradigmatic radical innovation—was the product of an attempt to provide a form of lighting that improved on existing methods for lighting the home, gas light (which constituted a fire hazard in domestic settings) and electric arc-light (which was too dazzling for domestic use and suffered from control and maintenance problems). Subsequent, incremental modifications of an original innovative product, process or system may, moreover, have vastly greater economic or social importance than the original product. For example, it was not until incremental advances in breakthrough microcomputer technology led to the personal computer revolution in the 1980s and beyond that the social and economic implications of the original invention began to be realized. Indeed, the US National Research Council has recognized that “[t]he cumulative effect of numerous minor incremental innovations can sometimes be more transformative and have more economic impact than a few radical innovations or ‘technological breakthroughs.’”¹¹

Incremental innovation has been an important source of India's recent economic growth and the recent success of Indian companies. A study of the role of innovation in the Indian economy carried out by the National Knowledge Commission (“NKC”) in 2007, which involved extensive interviews of representatives of pharmaceutical and other companies, determined that while 37.3% of Indian companies have introduced breakthrough innovations in recent years, no fewer than 76.4% *have introduced incremental innovations*. The

NKC further found that more than half of the innovation introduced by large companies in India that is “new to world” (i.e., that has never before appeared in any market) has been incremental in nature.

For example, incremental innovation has played an important role in improving treatments for diabetes patients. Due to peaks and troughs in insulin levels, diabetics must be cautious in the timing of

It is not uncommon for drugs based on incremental pharmaceutical innovations to be disparaged and dismissed as “me-too” drugs that provide little, if any, added value over existing drugs. However, a study conducted in 2007 of the medicines on the World Health Organization’s (WHO) Essential Drug List found that over 60% of the drugs on the list reflect incremental improvements of older drugs.¹² Notably, the criteria for inclusion on WHO’s list of essential drugs includes “evidence of efficacy and safety, as well as disease prevalence and comparative cost-effectiveness” of drugs.¹³

Indeed, there are countless examples of incremental pharmaceutical innovations across different drug classes and treatment categories—including antihistamines, beta-blockers, non-steroid anti-inflammatory drugs, diabetic drugs, anti-psychotics, treatments for hepatitis C, rheumatoid arthritis treatments, and oral contraceptives, among others—which demonstrate the potential clinical and social and economic value of such innovations.¹⁴ The following are just a few instructive examples:

- **Controlled-release drug delivery system using microspheres.** This innovation involves the novel use of glass-like microspheres made of sugar for the controlled-release of known drugs and vaccines. The microspheres are formed from sugars suspended in non-water containing liquids, which are dissolved and release the active drug very slowly over a considerable period of time. Among other advantages, the microspheres are capable of surviving temperatures as high as 55° Celsius for months, unlike normal vaccines.

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Like innovation in other fields, pharmaceutical innovation has both radical and incremental dimensions. Radical pharmaceutical innovation involves the often groundbreaking discovery of new molecules, and typically results in the creation of new “drug classes,” or groupings of drugs on the basis of a mechanism of action. Incremental pharmaceutical innovation, on the other hand, typically involves modification and improvement of existing drugs, resulting in a greater number of drugs within a given drug class. While the breakthrough discovery of penicillin is an example of a radical pharmaceutical innovation that gave rise to powerful new treatments for bacterial diseases and initiated a new field of pharmaceutical research focusing on antibiotics, the incremental discovery of antibiotics derived from penicillin, such as ampicillin, which offered a greater spectrum of activity than the original penicillins, or other antibiotics that are effective against types of bacteria that are resistant to other forms of penicillin, represent incremental innovations that have had powerful implications for the treatment of disease. Incremental innovations in the pharmaceutical industry also commonly appear as new dosing formulations, e.g., once-daily formulations, or new delivery systems, e.g., time-release delivery, for existing drugs, which can reduce toxicity and side-effects and otherwise improve the effectiveness and/or convenience of such drugs.

insulin administration. Short- and long-acting formulations have been developed that offer diabetic patients greater flexibility in their treatment schedules. The onset of action for short-acting insulin analogs can be as little as 15 minutes, compared with the 30 – 45 minutes of lead time required for regular insulin. At the other end of the spectrum, long-acting insulin analogs offer 24-hour peakless levels, thereby requiring only once-daily injections by the patient. These analogs, developed by substituting specific amino acids in regular insulin, significantly improve the patients’ quality of life, offering enhanced flexibility in their daily routines and/or freedom from multiple injections. Similarly, the discomfort and health hazards associated with injection-based treatments, including injection-site infections and difficulties in administering frequent injections to children and the frail and elderly, has recently spurred interest in the development of oral and inhalable formulations of insulin. These are incremental advances in insulin formulations that would greatly improve the quality of life of diabetics everywhere and would be especially valued in regions where the incidence of diabetes is high, such as the Indian subcontinent.

60% of the drugs on the World Health Organization’s Essential Drug List reflect incremental improvements of older drugs.

In addition, the microspheres may be used simultaneously for multiple vaccines, making possible injection of several vaccines at once. It has been estimated that this innovation could save up to US\$300 million per year in global vaccine costs simply by eliminating the need for refrigeration. Moreover, the ability to survive extreme heat conditions could enable more children in remote tropical areas to obtain vaccinations where use of normal vaccines might previously have been difficult.¹⁵

■ **Alternative salt forms of pyroloquinolines and benzoquinolizines.**

In 1983, patents were issued relating to these antibacterial compounds, which were described as effective against bacteria that were resistant to conventional antibiotics. However, the patented active substances had the disadvantage of having undesirable solubility characteristics in aqueous solutions, which made it difficult to formulate a drug in tablet or capsule form or in making injectable formulations. It was later discovered that certain salt forms of the original active substances have greater stability characteristics over the prior known substance in the presence of high humidity climates such as those prevalent in India, as well as more favorable toxicity values, among other benefits. Several US patents have been issued directed to these valuable incremental innovations, which have self-evident public health benefits in India and other sub-tropical developing nations.¹⁶

■ **Sulfonylurea anti-diabetic agents.**

Sulfonylureas are key medications in the treatment of diabetes and act by binding to ion channels on pancreatic cells, thereby stimulating the secretion of insulin. The first generation of these drugs was developed by modifying sulfonamide antibiotics

when researchers discovered that the compound sulfonylurea obtained from the antibiotics induced hypoglycemia, or low blood sugar, in experimental animals. The second generation of sulfonylureas were developed by changing the chemical structure of the side-chains. Modifying the side-chains did not alter the basic efficacy but significantly enhanced the selective binding of these second-generation sulfonylurea drugs to the pancreatic cells, which in turn resulted in greater potency at lower drug doses. Further, the side-chain modification of the second-generation sulfonylureas reduced drug-drug interactions and thereby lowered the incidence of adverse events, which conferred significant benefits on patients receiving multi-drug therapy. As a result of their improved potency and safety profiles, second-generation sulfonylureas have been adopted widely throughout the world, including India, as the drug of choice in this category of anti-diabetic agents.

■ **Cephalosporin antibiotics.**

The development of cephalosporin antibiotics demonstrates clearly the beneficial potential of incremental innovation. The first generation of cephalosporins was developed in the 1960s in order to respond to the emergence of antibiotic-resistant bacterial strains. Successive generations of cephalosporins, arrived at through incremental modification of the basic cephalosporin compound, are effective against different types of bacteria to different degrees and in different dosage forms. These differences enable a physician to calibrate treatment to the needs and circumstances of the individual patient and the underlying disease.¹⁷

■ **Once-daily ciproflaxin.**

Ciproflaxin is a broad spectrum antibiotic. A once-a-day formulation of ciproflaxin was recently developed

in which the active ingredient is released from two layers. The first releases ciproflaxin into the blood within hours. This is followed by a second extended release of the active ingredient to allow sustained levels over twenty-four hours. The novel formulation is more convenient for patients and results in greater patient compliance.¹⁸

■ **H2-receptor antagonists.**

The development of H2-receptor antagonists (“H2RA”) for the treatment of peptic ulcer disease, gastroesophageal-reflux disease, dyspepsia and other gastric conditions demonstrates successive waves of incremental innovation leading to a breakthrough drug. In the 1960s, it was discovered that histamine stimulates the secretion of stomach acid. After extensive experimentation, it was discovered that burimamide was an H2RA; however, it was insufficiently potent for oral administration. Further modification of burimamide led to the development of metiamide, which was effective but also associated with toxicity and side-effects. Further modifications resulted in the discovery of cimetidine, which became the first commercialized H2RA. Further modification of cimetidine led to the development of ranitidine (commercialized in the US as Zantac), which had fewer adverse drug reactions, longer-lasting action, and ten times the action of cimetidine.¹⁹

These examples indicate that incremental pharmaceutical innovation can improve the usefulness and effectiveness of existing drug products and result in less expensive and more accessible treatments. As such, incremental pharmaceutical innovation has important clinical and social and economic benefits, which we discuss below.

B. The Clinical Value of Incremental Pharmaceutical Innovation

Incremental pharmaceutical innovation can have the following clinical benefits: *increased effectiveness, extended usefulness, and greater selectivity.*²⁰

Incremental pharmaceutical innovations frequently result in increased effectiveness over prior known drug products. Breakthrough drugs often exhibit side-effects and other limitations that lead to their replacement by more effective, incrementally improved versions. Between 1960 and 2003, approximately one third of all drugs based on incremental advances approved by the U.S. Food and Drug Administration (“FDA”)—including new formulations, new combinations of active ingredients, and new salts or esters of approved compounds—received a “priority rating” from the FDA, which indicates that such drugs demonstrated *significant* improvement over existing drugs in one or more of the following ways: (1) evidence of increased effectiveness in the diagnosis, treatment or prevention of a disease; (2) elimination or substantial reduction of a treatment-limiting drug reaction; (3) documented enhancement of patient compliance; or (4) evidence of safety and effectiveness for a new patient subpopulation.²¹ This number, moreover, likely underestimates the extent to which the original breakthrough drug is not the best-in-class drug, as the FDA is unlikely to issue a priority rating for a relatively modest improvement in an existing chemical or pharmacological class.²² As

noted above, over 60% of the drugs on the WHO’s list of essential medicines reflect incremental improvements of older drugs.

Increased effectiveness often is the result of incremental advances in dose delivery systems and dosage forms, such as transdermal delivery and extended release formulations, which can optimize the rate of absorption of a molecule and thereby maximize its therapeutic effect, while reducing toxicity and side-effects.²³ Advances in dose delivery systems and dosage forms may also result in more convenient dosing schedules, which improve patient compliance and thus, indirectly, therapeutic value. Reformulations of existing drugs may also result in new applications for such drugs, which would extend their usefulness. For example, the reformulation of the corticosteroid budesonide, an asthma drug, into an inhalation suspension enabled the development of an asthma treatment for children. Prior to this advancement, no inhalers were available for children with asthma.²⁴

By increasing the number of drugs that exist within a given class, incremental innovations may result in greater drug selectivity. It is known that different people react differently to the same drug. Indeed, for some drug classes, response rates to individual drugs may be as low as 50%.²⁵ This is true, for example, of selective serotonin re-uptake inhibitors and non-steroid anti-inflammatory agents. Pharmacogenomic studies show that genetic factors play an important role in determining the efficacy of any given drug. Thus, different populations may have varying responsiveness to different

forms of a drug.²⁶ Having an array of drugs within a given class, each with different drug-drug interactions, adverse-effect profiles, adverse drug reactions, and dosing schedules, allows a physician to calibrate their prescription to the responsiveness and needs of an individual patient.²⁷ Multiple drugs within a given therapeutic class also provide important back-up in case a drug is taken off the market due to, e.g., unacceptable side-effects.²⁸

C. The Social and Economic Value of Incremental Pharmaceutical Innovation

In addition to the clinical benefits discussed above, incremental pharmaceutical innovation has important social and economic benefits. These include *increased resources for new drug discovery, reduced healthcare and other social costs and increased drug price competition.*²⁹

According to several estimates, the current cost of developing a breakthrough drug from discovery to market today may be as much as US US\$1 billion, if not more.³⁰ Moreover, this figure has been increasing as a result of increasing input costs associated with clinical trials and other R&D expenditures.³¹ New drug development is thus extremely costly; it is also highly risky, given that a drug that has been in development for several years may prove to be unsafe or otherwise fail to obtain regulatory approval. Commercialization of drug products based on incremental innovation provides the pharmaceutical industry with crucial revenue to support new drug discovery programs and mitigate the risks of new drug development. According to one study, the number of drug products approved by the US Food and Drug Administration (“FDA”) between 1989 and 2000 based on new uses or new forms of known substances comprised approximately 65% of all drug products approved by the FDA during that period.³² Indeed, patents

New drug products based on incremental pharmaceutical innovations accounted for about \$17 billion or about 38% of all new spending in the retail prescription drug market.

on new molecules represent only 10% of the total number of pharmaceutical patents issued annually.³³ Between 1995 and 2000, new drug products based on incremental innovations accounted for approximately US\$17 billion of new retail prescription drug spending in the United States, or approximately 38% of all new spending in the retail prescription drug market.³⁴ Commercialization of incremental pharmaceutical innovations thus can generate revenue that can help research-

class.”³⁶ As such, drug development is best understood as “development races” between pharmaceutical companies as opposed to “after-the-fact imitation” of proven drugs.³⁷ New molecule discovery and incremental pharmaceutical innovation thus increasingly occur in tandem.

Incremental pharmaceutical innovations have several other important social and economic benefits, including the reduction of healthcare and other social

introduced between 1995 and 1999 were launched at a discount over the price leader and 65% were discounted from the average price for the class of drugs as a whole. On average, incremental drugs were introduced at a 26% discount over the price leader and a 14% discount relative to the class average.³⁹ The data further suggests that the price-constraining effect of incremental innovation on drug prices is likely to be greater in markets where price-competition is generally stronger.⁴⁰

About 65% of all drug products approved by the FDA between 1989 and 2000 were based on new users or new forms of known substances.

based pharmaceutical companies fund the high cost of new drug development. Investment in incremental R&D can also have a “spillover effect” in that R&D undertaken with respect to incremental pharmaceutical innovation may result in efficiencies with respect to new molecule discovery, and vice versa.³⁵

Recent studies of the economics of drug development confirm the interrelatedness of breakthrough and incremental innovation. One recent study determined that the average length of time from a new drug approval to the launch of drugs based on incremental innovation has fallen dramatically, from 10.2 years in the 1970s to 1.2 years in the late 1990s, and that the majority of incremental drugs created in the 1990s were in clinical development prior to the approval of the breakthrough drug. The study concludes that, as a practical matter, the distinction between breakthrough drugs and incremental drugs may be meaningless, as “the prevailing drug development paradigm is one in which a number of firms will pursue investigational drugs with similar chemical structures of the same mechanism of action before any drug in the class obtains regulatory marketing approval. One of the drugs will win the race, and then be viewed as the breakthrough drug for the

and economic costs. At the individual patient level, incremental pharmaceutical advances can reduce overall treatment costs by increasing drug bioavailability and reducing the dosing frequency. Incremental advances improve patient compliance by reducing side-effects and toxicity and creating more convenient formulations, which in turn reduces costs associated with extended treatment schedules. In addition, more effective treatment options and improved patient compliance can result in the need for fewer hospital stays or physician visits.

At the macro level, incremental pharmaceutical innovations can reduce employee absenteeism and mitigate the impact of illness on labor productivity.³⁸ Incremental pharmaceutical innovation can also increase competition within the pharmaceutical industry and reduce drug prices. One study of the US market demonstrated that as much as 80% of new drugs based on incremental advances

Finally, by expanding the number and diversity of drug products on the market, incremental pharmaceutical innovation also benefits the generic industry as it makes available a greater range of products for potential generic marketing once applicable patent protection, if any, has expired.

II. THE BENEFITS OF INCREMENTAL PHARMACEUTICAL INNOVATION FOR INDIA—AND THE NEED FOR ADEQUATE INCENTIVES

The preceding discussion of the clinical, social and economic benefits of incremental pharmaceutical innovation suggests that such innovation can have important advantages for Indian patients and Indian businesses.

As much as 80% of new drugs based on incremental advances introduced between 1995 and 1999 were launched at a discount over the price leader and at a 26% discount.

Some Of The Benefits Of Incremental Pharmaceutical Innovation For India

- Improved quality of drug products in India, including products that are better suited to India's climate.
- Development of treatments for diseases that are prevalent in India for which new drug discovery is currently limited or otherwise inadequate.
- Increasing likelihood that for every therapeutic class, there is a treatment to which an Indian patient will respond.
- Development of the R&D capacity and expertise of Indian pharmaceutical companies.
- Reduction of healthcare and other social costs in India through improved drug quality and selection.
- Increased access to medicine as a result of price competition.

First, incremental pharmaceutical innovation can improve the quality of drug products in India. For example, incremental innovation can result in formulations and drug delivery systems that are better suited to India's climate, such as those involving the use of microspheres in vaccines or salt forms of pyroloquinolines and benzoquinolizines, which maintain stability under high humidity.

Second, incremental pharmaceutical innovation can potentially lead to the development of treatments for diseases prevalent in India, such as tuberculosis, malaria and other tropical diseases, for which new drug discovery is currently limited or otherwise inadequate, based on the investigation of new forms or new uses of known substances.

Third, by increasing the treatment options within a given therapeutic class, incremental pharmaceutical innovation would increase the likelihood that, for every therapeutic class, there will be a treatment to which an Indian patient will respond.

Fourth, engaging in incrementally innovative activity can enable Indian pharmaceutical companies to develop their innovation expertise and to benefit from R&D spillover effects and synergies as they move increasingly into the discovery of new compounds. Moreover, the commercialization of incremental innovations by Indian pharmaceutical companies will provide revenue that can help fund the development of research labs devoted to new compound discovery and further incremental innovation. As noted, drug products based on incremental innovations account for as much as one-third of the retail market for new drugs in the United States. The Indian pharmaceutical market is expected to be worth as much as US\$20 billion by 2015.⁴¹ Incremental pharmaceutical innovations could thus account for a

substantial share of this market—potentially as much as US\$7 billion. As such, incremental pharmaceutical innovation can be an important source of revenue for Indian companies and a key stepping stone for Indian pharmaceutical companies to become leaders in the discovery of new compounds.

Fifth, incremental innovation can help reduce healthcare and other social costs in India by improving the quality and selection of drug products and thereby reducing demands on scarce resources resulting from extended hospital stays and frequent doctor's office visits and diminished productivity due to illness and worker absenteeism.

Sixth, incremental pharmaceutical innovation can increase drug price competition in India, especially given the highly competitive nature of the Indian pharmaceutical market, and thus reduce price and increase access to medicine. Incremental innovation could also benefit the Indian generic industry as more products would be potentially available for generic marketing.

To realize these and other benefits, however, Indian pharmaceutical companies must be willing to engage in incremental pharmaceutical innovation in the first place. There is a general perception that incremental innovations are based on easy or trivial modifications of existing inventions and that they involve no real risk or effort to develop.⁴² From their sheer ingenuity alone, the examples of incremental innovation discussed above suggest that this is not the case. Economic analyses confirm that incremental pharmaceutical innovation involves considerable investment of time and money. One study of the cost of developing new drugs estimates that R&D associated with improvements and modifications of a drug constitute more than 25% of all out-of-pocket R&D expenditures of US

pharmaceutical companies—on average, US\$140 million out of US\$540 million.⁴³ Another study estimates that 30% of US industry R&D spending is devoted to new or modified uses for existing products.⁴⁴ A third estimate proposes that R&D expenditure associated with incremental pharmaceutical innovation can be estimated at between 25% and 50% of the R&D expended on new drug discovery.⁴⁵ As in the case of new compound research, the continued development of incremental innovations in the pharmaceutical industry requires adequate incentives for companies to undertake the required levels of investment and risk. As we shall see below, India's patent law regarding incremental pharmaceutical innovation provides little, if any, incentives for Indian companies to undertake such effort and investment.

III. INCREMENTAL PHARMACEUTICAL INNOVATION UNDER SECTION 3(d) OF THE INDIAN PATENTS ACT

India's patent law recently underwent a major transformation resulting from India's membership in the World Trade Organization ("WTO"). Among other things, this resulted in the establishment of patent protection for pharmaceutical products. While this has played—and will continue to play—an important role in facilitating India's emergence as a global innovator, India's reluctance to provide patent protection for incremental pharmaceutical innovation deprives India of the full benefits of such innovation discussed above and threatens to hold India back from continued economic expansion.

A. Background: Pharmaceutical Products Under India's Patent Laws Prior to 2005

India enacted its first patent law in 1856 while still under British rule. Though it was amended several times during the colonial period, India's patent law consistently provided for the patenting of pharmaceutical products. After gaining Independence in 1947, however, India undertook a systematic review of its patent law aimed at developing its domestic pharmaceutical industry, which culminated in the Patents Act of 1970. The 1970 Act, which came into effect in 1972, limited patent rights in several important ways. Most importantly, the 1970 Act precluded the patenting of pharmaceutical products—the Act provided that for inventions relating to food, medicine, drugs or chemical substances, only patents relating to the methods or process of manufacture of such substances could be obtained. The 1970 Act also permitted an applicant to patent no more than a single process for making a pharmaceutical product and reduced the term for such process patents from 14 years to the shorter of five years from the date of patent approval or seven years from the date of application. In addition, the Patents Act provided for broad compulsory licensing of pharmaceutical process patents starting from three years after the date of issuance with payment of a royalty.

With patent protection still available for methods of making pharmaceutical products, under the 1970 Act, a large generic pharmaceutical industry emerged in India, which developed the ability to reverse-engineer pharmaceuticals developed and patented outside of India and design new processes for producing such drugs. Under this new patent regime, the

number of drug manufacturing facilities grew from 2,257 in 1970 to over 23,000 in 2005.⁴⁶ The Patents Act of 1970 provided little incentive, however, for pharmaceutical companies in India to perform original research and develop new drugs. Between 1970 and the 1990s, Indian pharmaceutical companies spent on average less than 0.2% of their sales on research and development.⁴⁷ Much of this investment was, moreover, directed largely at reverse-engineering rather than new product development. Nor did Indian pharmaceutical companies file patent applications during this period, either in India or abroad. As a result of the changes brought by the 1970 Act, the number of patents granted per year fell by three-quarters over the following decade, from 3,923 in 1970-71 to 1,109 in 1980-81. Between 1980 and 1984, Indian inventors accounted for only 0.09% of all pharmaceutical patents issued by the US Patent Office.⁴⁸

In 1995, India became a founding member of the WTO and a party to the WTO's Trade-Related Aspects of Intellectual Property Rights ("TRIPS") Agreement. Among other things, the terms of the TRIPS Agreement required India to provide patent protection for pharmaceutical products by January 2005. India purported to comply with this and other TRIPS obligations through a number of patent law amendments culminating in the passage of the Patents (Amendment) Act, 2005 on April 5, 2005, with retrospective effect from January 1, 2005.

Among other impact of the 2005 amendments, the number of patent filings in India for pharmaceutical products has increased steadily. The total number of patents granted in India jumped from 1,911 in 2004 – 05 to 4,320 in 2005 – 06, with the number of patents issued to Indian residents increasing by nearly 100%.⁴⁹ Since 2005, roughly 33% of

all patent applications filed in India have been directed to chemicals and/or drugs, and five of the top ten domestic filers of patent applications are Indian pharmaceutical companies.⁵⁰ In addition, the new protections for pharmaceutical products and other protections provided by the 2005 amendments have increased foreign direct investment (“FDI”) in the Indian pharmaceutical sector. In anticipation of the new law, pharmaceutical FDI increased sharply in 2004, declined in 2005 and then rebounded in 2006.⁵¹ Strategic alliances between foreign and domestic companies in the areas of clinical trials, new drug discovery, and the manufacture of drugs and drug components have also increased.⁵²

B. Section 3(d): New Forms of Known Pharmaceutical Substances

Despite the apparent paradigm-shift reflected in the 2005 amendments, those amendments did not uniformly provide patent protection for *all* pharmaceutical innovation in India. On the contrary, the 2005 amendments preclude patent protection for new forms or new uses of known pharmaceutical substances that do not result in the “enhancement of the known efficacy of that substance.”⁵³

In order to obtain a patent in India, an applicant must demonstrate that his or her claimed invention constitutes patentable subject matter and meets three basic requirements of patentability. With respect to patentability requirements, the applicant must show, first, that the claimed invention is *novel*; second, that the claimed invention is non-obvious or involves an *inventive step*; and third, that the claimed invention has *industrial application*. In addition to meeting such patentability requirements, an applicant must also show that the claimed invention constitutes *patentable subject matter*. In India, the categories of non-patentable subject matter include the laws of nature;

subject matter that is contrary to public morals; mathematical methods and scientific theories; plants and animals; a method of agriculture; and a method of medical treatment.⁵⁴

Section 3(d) of the 2005 Act added to the list of non-patentable subject matter new forms and new uses of known substances. Specifically, Section 3(d) provides that the following is not patentable:

[T]he 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* or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.⁵⁵

The “Explanation” accompanying this provision indicates that Section 3(d)’s exclusion from patentable subject matter is meant to apply broadly to all derivatives of a known substance unless they differ “significantly” with respect to “efficacy”:

For the purpose of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substances shall be considered to be the same substance, *unless they differ significantly in properties with regard to efficacy*.⁵⁶

While the statute does not define the terms “significantly” or “efficacy,” under Section 3(d), any incremental pharmaceutical innovation involving a new form (or other derivative) or a new use of a known substance that does not meet the standard implied by these terms is not patentable. As discussed further below, there is good reason to believe

that both the Indian patent office and Indian courts take the view that “efficacy” is to be understood narrowly to mean “therapeutic efficacy.”

At the time the Indian government was preparing to implement its obligations under TRIPS, opponents of pharmaceutical product patents argued that product patents would reduce access to life-saving drugs and would permit patent evergreening. Shri Suresh Kurup expressed this view during the parliamentary debates in the Lok Sabha:

SHRI SURESH, KURUP (Kottayam): Respected Deputy-Speaker, Sir, ever since this Patents (Amendment) Ordinance was promulgated, widespread apprehensions were expressed by groups concerned in India and also outside the country about the provisions of the Bill. The concern was due to the fact that it will *prevent the common man in our country and also of the other developing and least developed countries having access to the life-saving medicines*.

One major area where all of us have raised our criticism was *the provision which helps the patent holder multinational companies for ever greening of patents*. Sir, a company which obtains a patent by changing their chemicals, before the expiry of the patent, they will again apply for a patent and again get a patent. So, in this way, they will continue to get a patent for the same medicine...⁵⁷

Proponents of Section 3(d) argued that the section was necessary to prevent patent evergreening and to prevent the escalation of Indian drug prices.

Section 3(d) states that the following is not patentable:

[T]he 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* or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.

The “Explanation” that accompanies Section 3(d) states:

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

In contrast, those who opposed Section 3(d) and were in favor of broad patent protection argued that patent protection for incremental pharmaceutical innovation would benefit Indian pharmaceutical companies by creating incentives for such companies to invest in incremental innovation and become global leaders in this area. This perspective was advanced by Shri Kharabela Swain during the parliamentary debates:

SHRI KHARABELA SWAIN:
I very strongly support that India should have a very strong patent regime. It is not to protect the patents of the multinationals, but it is to protect the patents of the Indians and the Indian companies.

Sir, the point is that India requires a very strong patent regime to attract FDI. Without it, we cannot attain sustainable growth of eight per cent over the years. So, we require it. Most of the time we oppose [product patents] with the thought that patent belong to the multinationals, and it has got nothing to do with the Indians. It is not true. *It is the Indians who are putting a lot of money in research and development with regard to medicines, bio-technology, rocket-making, etc. These have to be protected. If we do not have a strong patent regime, the moment we invent something new, foreigners will copy that. Do you not want that our scientists should be benefited? Do you not want that their patents should be protected? They should also earn some money out of that. Do you not want that? We wanted that... India could also be a hub of research and development. It is possible because the cost of research and development is much less in India. If you develop a*

molecule, a new thing it costs much cheaper in India. Therefore, we can attract foreigners here. They can come and make India a hub.

I will be very brief on two points. I will not make a long speech. The very first thing is incremental innovations. Most of the time we say that patents will become evergreen. It is because probably somebody who has got a patent on some molecule, may go for some new usage. The Hon. Minister has explained in his amendments with regard to those things. I am opposing it. My point here is that the cost of medicines was cheap in India. It was only because of reverse engineering. There was a process patent available in our country. So, if any foreign company produced any medicine, our scientists could found [sic] out a different method of producing the same medicine at a much cheaper cost. That is why the medicines are much cheaper here. It was not very easy to do that. This reverse engineering process was not so easy. Had it been so easy, every country would have adopted this method. It was possible because our scientists were intelligent enough to take to this reverse engineering and made it successful all the time. This incremental innovation is only one or two steps away from that. If we do not allow it and say that we will go only for molecules, how many companies are capable of bringing out new molecules? For bringing out a new molecule, you require Rs. 6,000 crore. How many Indian companies will have this much of money? *So, if we allow these incremental innovations, it is not only the multinationals, but also the Indian companies who will benefit out of it.*⁵⁸

Opponents of Section 3(d) further argued that encouraging incremental innovation by domestic pharmaceutical companies would lead to the development of drug products tailored to the needs of Indian patients.⁵⁹ Nonetheless, the proponents of Section 3(d) won the day, and that provision was enacted as a political compromise to temper what anti-intellectual property advocates argued were the negative effects of pharmaceutical product patents.⁶⁰

C. The Meaning of “Efficacy”

The first significant application of Section 3(d) occurred shortly after the 2005 amendments were enacted, when the Assistant Controller of Patents rejected Novartis’ application for a patent relating to the drug product Glivec, used in treating chronic myeloid leukemia (“CML”) and gastrointestinal stromal tumors (“GIST”). The court decisions relating to Novartis’ patent application for Glivec confirm that the scope of incremental pharmaceutical innovations that constitute patentable subject matter under Section 3(d) is severely restricted and highlight the narrow meaning of “efficacy” as it is used in the context of Section 3(d).

In the 1980s, after two decades of research, Novartis scientists discovered a drug compound, “imatinib,” that targeted a cancer-causing enzyme involved in CML but without disrupting other enzymes in a healthy cell. Novartis applied for a US patent on this compound and all pharmaceutically acceptable salts of the compound in 1993. Further research into imatinib led to the discovery that a particular “polymorphic form” of a particular salt form of the compound was the most stable version of the compound. This version, the beta crystalline form of imatinib mesylate, became the active ingredient for the drug, Glivec (also known as “Gleevec” in the United States), which was approved by the FDA in 2001.

Novartis has obtained approximately 40 patents around the world covering the active ingredient in Glivec.⁶¹

In 1998, Novartis filed a patent application in India relating to the active ingredient in Glivec pursuant to features of India’s patent law that enabled applicants claiming pharmaceutical inventions prior to 2005 to be filed and stored until examination in 2005—so-called “mailbox applications.” Novartis launched Glivec in India in 2002 and also applied for and received an exclusive marketing right relating to Glivec pending the grant of its patent. After the 2005 amendments were passed, Novartis’ mailbox application was opened and examined. Several generic drug companies, among others, opposed the application on numerous grounds including that the claimed invention did not demonstrate significantly enhanced efficacy required under Section 3(d). The Assistant Controller of Patents rejected the patent application on this and other grounds.

During these proceedings, Novartis argued that its application was not barred by Section 3(d) because the active ingredient in Glivec, the polymorphic, salt form of imatinib, was more effective than the “known” imatinib-free base in so far as it was absorbed more easily into the bloodstream and thus displayed better bioavailability. Specifically, Novartis argued that the new form of imatinib increased bioavailability by 30%. However, the Assistant Controller held that this did not constitute a sufficient increase in efficacy under Section 3(d), with little explanation or analysis of Section 3(d) itself.

In 2006, Novartis launched an appeal to the Madras High Court seeking (1) a reversal of the Assistant Controller’s rejection of Novartis’ application; and (2) an order declaring Section 3(d) unconstitutional and in violation of TRIPS. The High Court transferred the first issue to the Intellectual Property Appellate Board (“IPAB”), which is currently pending.

With respect to Novartis’ challenge to the TRIPS-compliance of Section 3(d), the Madras High Court ruled that it did not have jurisdiction over the issue, and noted that the WTO Dispute Settlement Body would be the proper forum for such a dispute. Novartis did not pursue the issue further and this remains an open issue.

In its challenge to the constitutionality of Section 3(d), Novartis argued that the usage of terms such as “enhancement of known efficacy” and “differ significantly in properties with regard to efficacy,” without accompanying guidelines, rendered Section 3(d) vague and arbitrary. Novartis further argued that because of the lack of such guidelines as to the scope of such terms, Section 3(d) vested the Indian patent office with unfettered discretion to devise its own policy as to what constituted a significant enhancement of efficacy. The High Court, however, rejected these arguments on the basis of established Indian constitutional principles, finding, among other things, that any determination employing the challenged statutory language is likely to be based on materials submitted by the applicant to the patent office and would be appealable, and that what amounts to a significant enhancement of efficacy depends on the facts of each specific case. In reaching this decision, the High Court relied upon a particular dictionary definition of the term “efficacy” in terms of “therapeutic efficacy.” For example, the Court stated that “if the discovery of a new form of a known substance must be treated as an invention, then the Patent applicant should show that the substance so discovered has a better *therapeutic* effect.”⁶²

The High Court’s decision increases the probability that Section 3(d) will be interpreted restrictively by Indian courts and the Indian patent office to permit patenting of an incremental pharmaceutical innovation only when it results in significantly enhanced *therapeutic* efficacy, but not if the innovation has some other advantage or beneficial effect,

e.g., better stability in humid conditions or more convenient administration. This is further confirmed by the Delhi patent office's rejection under Section 3(d) of a patent application submitted by Boehringer Ingelheim directed to a new HIV composition because Boehringer did not demonstrate significantly enhanced "therapeutic efficacy" over the previously known compound.⁶³ Similarly, the Chennai patent office recently refused Novartis' application directed to the alpha crystal form of imatinib mesylate in part on the basis that there was no evidence of "therapeutic efficacy" over the known form of the substance even though there was evidence of a 20% increase in bio-availability.⁶⁴ In addition, the guidelines regarding Section 3(d) set forth in the current Manual of Patent Practice & Procedure, which are relied upon by patent examiners during examination of a patent application, quote the Madras High Court's definition of efficacy, including its reference to "therapeutic efficacy." This also suggests that patent examiners are likely to apply the therapeutic standard in examinations.

Finally, it is worth noting that the language of Section 3(d) itself was based on a provision of a European Union Directive relating to the regulatory approval of drug products for human use. Article 10(2)(b) of Directive 2004/27/EC defines a "generic medicinal product" as:

a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. *The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with*

regard to safety and/or efficacy. In such cases, additional information providing proof of the safety and/or efficacy of the various salts, esters or derivatives of an authorised active substance must be supplied by the applicant. The various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form. Bioavailability studies need not be required of the applicant if he can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate detailed guidelines.⁶⁵

Significantly, this EU Directive relates to the regulatory drug approval. It does *not* purport to define the scope of patentable subject matter or otherwise exclude incremental pharmaceutical innovations from the subject matter for which a patent may be issued in the European Union (as indicated below, incremental pharmaceutical innovations are patentable in Europe). The fact that Section 3(d) was based upon an EU Directive that relates to the regulatory drug approval process for generic products and the underlying notion of "bioequivalence" further supports the view that the concept of "efficacy" in Section 3(d) will be construed narrowly in terms of "therapeutic" efficacy rather than in broader terms.⁶⁶

Thus, to demonstrate that a new form or use of a known substance qualifies for a patent under Section 3(d) because it differs "significantly" with respect to the known "efficacy" of the substance, a patent applicant must produce data demonstrating the therapeutic efficacy of the new form or use. This is a very difficult burden to meet without engaging in the sort of clinical investigations that normally are not conducted until much later in the drug-development process. This threshold burden is likely to have a significant impact on Indian pharmaceutical companies in particular as it is likely to force such companies to look to markets other than India with no such efficacy requirement to

develop and commercialize drug products based on incremental innovations. Section 3(d) thus discourages Indian companies from investing in product development for their home market. As a result, Section 3(d) decreases the likelihood that Indian companies will develop products geared to the needs of Indian patients.

Moreover, even if such clinical efficacy data were available at the patent application stage, the absence of adequate data protection rules for clinical data in India provides a strong disincentive for patent applicants to disclose such data to the patent office. Finally, it is unclear that patent examiners possess the expertise necessary to make determinations of comparative therapeutic efficacy, which is normally a matter for the drug regulatory agencies.

It should be noted that the IPAB heard Novartis' appeal in the Glivec case at the end of 2008 but has not yet issued its ruling on the matter. It is possible that this decision will provide some additional guidance as to the meaning of "enhanced efficacy" under Section 3(d). However, it is likely that the IPAB will be guided, at the very least, by the High Court's analysis of this language and its understanding of "efficacy" in terms of "therapeutic efficacy."

D. Section 3(d) in International Context

The current case law interpreting Section 3(d) and the Manual of Patent Practice & Procedure thus confirm the view that, presently in India, incremental pharmaceutical innovations are eligible for patenting only in very rare circumstances. When it enacted Section 3(d), India was the only country in the world to adopt this view and categorically exclude from patentable subject matter inventions directed to new uses or new forms of known pharmaceutical substances. Today, India remains one of the only countries in the world to take such

an approach towards incremental pharmaceutical innovation.⁶⁷ By contrast, the patent laws of other jurisdictions and the international norms embodied in the TRIPS Agreement together reflect a general international consensus that incremental pharmaceutical innovations are valuable to societies and should therefore be rewarded and encouraged through patent protection.

The patent offices of other developing nations, such as Brazil and China, do not treat patent applications directed to incremental pharmaceutical innovations differently in principle than applications relating to breakthrough drugs or other inventions. Indeed, it is reported that in China most of the 56,769 patent applications filed by domestic applicants between 1985, when the China patent system came into force, and 2003 were directed to incremental innovations, including incremental pharmaceutical innovations, and represented the realization of a previously untapped source of innovation for the Chinese economy.⁶⁸

Both Japan and Italy recently underwent the very transition that India is presently undergoing when they adopted patent protection for pharmaceutical patents and did so without an exclusion for incremental pharmaceutical innovations. In Italy, the transition to a system of product patents led to stronger Italian pharmaceutical companies, greater investment in domestic R&D, and increased foreign direct investment, among other benefits.⁶⁹ Similarly, studies of the Japanese experience note that the development of incremental innovations by Japanese companies soon after the transition to a product patent regime was instrumental in facilitating the ability of Japanese companies to later engage in other types of innovative activity, including new drug development.⁷⁰

The patent offices of the United States, Canada, the United Kingdom and Australia also routinely grant patents to

incremental pharmaceutical innovations provided the application is otherwise directed toward patentable subject matter and meets the requirements of novelty, non-obviousness/inventive step, and utility/industrial application.⁷¹ Similarly, the European Patent Office also grants patents directed to incremental pharmaceutical innovations.⁷²

The experiences of countries such as Japan, China and Italy confirms the view that intellectual property harmonization can contribute significantly to economic growth. Such countries recently amended their patent laws to bring them in line with nations such as the US, Canada, the UK and Australia and experienced resulting increases in economic opportunities. The experience of such countries also indicates the value of maintaining consistent protection for innovation across different industries and fields. India's inconsistent treatment of incremental innovations in the pharmaceutical industry could prevent it from realizing the full potential for trade with other nations and opportunities for partnerships with non-Indian pharmaceutical companies relating to the development of new pharmaceutical innovations. The impact of India's treatment of incremental pharmaceutical innovation on trade relations is thus similar to the impact that would result if another country adopted a patent law that precluded patents for incremental innovations in areas of innovation in which India has developed a competitive advantage, such as aerospace or automotive technologies, which would reduce the incentive for Indian companies to commercialize their products in that country.

The principle of non-discrimination among types of invention or fields of technology is reflected in Article 27.1 of the TRIPS Agreement, which states, in pertinent part, that "patents shall be available for *any inventions, whether products or processes, in all fields of technology*, provided that they are new, involve an inventive step

and are capable of industrial application... [P]atents shall be available and patent rights enjoyable *without discrimination as to the place of invention, the field of technology* and whether products are imported or locally produced." The "enhanced efficacy" requirement in Section 3(d) is not provided for in TRIPS, which exhaustively enumerates the circumstances under which WTO Members must make patent protection available. Indeed, the discovery of a new form of a known pharmaceutical substance may fulfill all of the TRIPS requirements for patentability as an invention—novelty, inventive step (or non-obviousness) and industrial application—irrespective of whether it results in the "enhanced efficacy" of the substance. As such, the India Patents Act's categorical exclusion of incremental pharmaceutical innovation from patentable subject matter appears *prima facie* to be in conflict with the international consensus reflected in the TRIPS Agreement that all innovations, regardless of field of technology, should be accorded equal protection and encouragement under national patent laws.

E. Implications of Section 3(d) for Incremental Pharmaceutical Innovation in India

Section 3(d) thus stands in stark contrast to much of the rest of the world, which does not so exclude incremental innovations from patentable subject matter. By restricting patentable subject matter to those incremental pharmaceutical innovations for which an inventor can demonstrate significant therapeutic enhancement over a known pharmaceutical substance, Section 3(d) excludes from patentable subject matter the vast majority of highly useful incremental pharmaceutical innovations. Under the Section 3(d) standard, the discovery of, for example, a new form of a known antibacterial compound that

retains stability in high humidity or a new combination of known compounds that results in a more effective, once-daily antibiotic drug that is cheaper for patients would not be eligible for patenting.

Significantly, Section 3(d) is also fundamentally at odds with the views and practices of Indian inventors and innovative pharmaceutical companies. Ranbaxy, for one, has publicly stated that:

As India's leading Pharmaceutical Company committed to R&D in the field of drug development, we are of the opinion that incremental innovations in terms of developing new forms, new derivatives and new delivery systems of existing drug should be granted patent protection provided they are new, involve an inventive step and have commercial utility. This will provide the necessary fillip to development of Novel Drug Delivery System (NDDS) in our laboratories.

Restricting patentability to [new chemical entities] may appear to be an attractive solution in the short-term to companies with a "Reverse—Engineering" mindset, but will not benefit hundreds of scientists working in our public and private R & D Centers, who are just starting off on the difficult task of new drug discovery research.

Restriction of patentability to [new chemical entities] alone is likely to benefit only MNCs which have the resources and the experience to develop [new chemical entities]. Indian companies that have far less resources are better placed to benefit from early commercialization of incremental innovations. A prerequisite to successful licensing deal for such products is the protection of the IP in the form of a patent, preferably in the country itself since products are being manufactured here.⁷³

Ranbaxy has also expressed the view that the "strength of Indian scientists lie[s] in innovations that improve existing products."⁷⁴

Similarly, the Organization of Pharmaceutical Producers of India ("OPPI") has expressed the view that excluding incremental pharmaceutical innovations from patent protection "would have significant negative consequences for the discovery and developments of future treatment for all disease areas and also will be an area of concern to all investors, domestic and foreign, because of the precedent it sets for the treatment of Intellectual Property in India."⁷⁵

Consistent with these pronouncements, Indian pharmaceutical companies have filed hundreds of patent applications directed to incremental pharmaceutical innovations in countries outside of India, as was noted by the technical expert committee chaired by intellectual property expert R.A. Mashelkar that the Indian government established to assess issues relating to India's new patent laws (the "Mashelkar Committee").⁷⁶ The Mashelkar Committee found that, among other things, incremental pharmaceutical innovation could play an important role in enabling Indian pharmaceutical companies to become innovators.⁷⁷ Indian companies such as Natco Pharmaceuticals, Aurobindo Pharma Limited, Morepen Laboratories, Ranbaxy, and Wockhardt Research Centre, among others, are already seeking to patent and commercialize outside of India incremental pharmaceutical innovations involving, among other things, novel combinations, formulations and polymorphs of known pharmaceutical substances, including the following:

- A new combination of olanzapine (a well-known drug used in the treatment of schizophrenia), a lubricating agent, a filler, and an agent that makes the drug rapidly disintegrate in the

In its submission to the Mashelkar Committee, Ranbaxy stated that:

"...we are of the opinion that incremental innovations in terms of developing new forms, new derivatives and new delivery systems of existing drug should be granted patent protection provided they are new, involve an inventive step and have commercial utility."

The Organization of Pharmaceutical Producers of India stated to the Mashelkar Committee that excluding incremental pharmaceutical innovations from patent protection:

"would have significant negative consequences for the discovery and developments of future treatment for all disease areas and also will be an area of concern to all investors, domestic and foreign, because of the precedent it sets for the treatment of Intellectual Property in India."

mouth of the patient, developed by Aurobindo Pharma Limited. The result of the combination is a drug that is easier to administer because it is rapidly dissolving and can be administered without water—an advantage for patients with difficulties in swallowing and patients that are uncooperative.

- A polymorph of atorvastatin (which is a well-known member of a class of drugs known as statins that are used extensively in the treatment of cholesterol) developed by Morepen Laboratories. The new polymorph is said to possess higher purity and stability than known forms of atorvastatin, thereby facilitating storage and improving yield during its production.
- Novel crystalline forms of rizatriptan (a well-known drug used in the treatment of migraine), developed by Natco Pharmaceuticals, are stable, reproducible, and suitable for pharmaceutical preparations.
- A combination of oxycodone, a well-known opioid analgesic, with a polymer that controls and extends the release of the drug, developed by Ranbaxy. The formulation is said to be easy to manufacture on a commercial scale and to enable the production of an extended release formulation in a cost-effective manner.
- A new formulation of vancomycin (a well-known antibiotic used in the treatment of serious infections) in hard gelatin capsules for oral administration developed by Wockhardt. Among other things, the new formulation is easier to handle and cheaper to produce compared to other available dosage forms of vancomycin.

The Appendix describes a small sample of such incremental pharmaceutical innovations developed by Indian pharmaceutical companies, for which

patent protection is being sought outside of India. *Innovations such as these are potentially precluded from patent protection in India because of Section 3(d).*

IV. REFORMING THE PATENTS ACT TO REALIZE THE BENEFITS OF INCREMENTAL PHARMACEUTICAL INNOVATION

The preceding sections suggest that the case for reforming Section 3(d) is strong. Under Section 3(d), the vast majority of incremental pharmaceutical innovations—including those currently being developed by Indian pharmaceutical companies for patenting abroad—are not eligible for patenting, especially in light of the Madras High Court’s interpretation of “efficacy” in terms of therapeutic efficacy. Therefore, if India is to take advantage of the benefits and opportunities presented by incremental pharmaceutical innovation, reform of Section 3(d) is necessary. We discuss options for reform below, but we first address a threshold issue regarding the interpretation of Section 3(d).

It has been argued that Section 3(d) does nothing more than create a *rebuttable presumption* that inventions directed at new uses or new forms of known substances are not patentable.⁷⁸ The argument goes that under Section 3(d) incremental pharmaceutical innovations are presumed to be ineligible for patenting; however, in any given case, evidence of significantly enhanced efficacy over a prior known substance will rebut that presumption and establish patent eligibility. On this theory, Section 3(d) functions in much the same manner as the principle of *prima facie obviousness* in US, UK and European patent law. In the United States, for example, a chemical compound that bears a very

close structural similarity to a known chemical compound may be determined to be obvious in view of the latter based on the expectation that compounds that are similar in structure will have similar properties.⁷⁹ However, an applicant can overcome this presumption by presenting evidence of “unexpected or surprising results.”⁸⁰ A similar rule exists in UK and European patent law.

The assumption that animates this interpretation of Section 3(d) is the view that incremental innovations should not be patentable because they tend to involve “trivial” modifications that would be obvious to someone with ordinary skill in the art. One proponent of Section 3(d) recently provided the following example to support this point:

if one is making a tablet of a product and then develops a paediatric dosage by way of a serum, this is not innovation *because any person skilled in chemistry knows how to make that...*⁸¹

Opponents of incremental pharmaceutical innovation thus argue that such innovations are inherently non-inventive—that they are, as a general rule, obvious to one with ordinary skill in the applicable art. From this perspective, Section 3(d) merely establishes a general statutory presumption to this effect, which may be rebutted with appropriate evidence of significantly enhanced efficacy.

There are several points to be made regarding this interpretation of Section 3(d). First, as we have seen above, far from being merely trivial and “easy,” incremental pharmaceutical innovations often involve considerable innovation and inventive effort. The assumption that all incremental pharmaceutical innovation is inherently trivial and obvious is thus without merit. Second, non-obviousness is a criterion of *patentability* not *eligibility for patenting*. As such, non-obviousness, along with novelty and industrial application, characterize whether a

Section 3(d) potentially precludes the patenting of hundreds of incremental pharmaceutical innovations that Indian companies are attempting to patent and commercialize outside India.

claimed invention *is in fact inventive* and thus patentable. Section 3(d), on the other hand, purports to limit the subject matter that is eligible for patenting, and states that incremental innovations that do not result in significantly enhanced efficacy are not eligible. The question of whether the subject matter claimed in a patent application is eligible for patenting at all is a threshold determination that is made before any assessment of whether a claimed invention meets the criteria of patentability. In fact, under Section 3(d), a claimed invention could meet the criteria of patentability, i.e., be novel, non-obvious and have industrial application, but nonetheless be ineligible for patenting because it is directed to non-patentable subject matter. In other words, under Section 3(d), an incremental pharmaceutical innovation may be truly inventive (i.e., novel and non-obvious) but nonetheless be ineligible for a patent because it is directed to a new form or use of a known substance.

Third, under the rule applicable in the US, to establish *prima facie* obviousness based on structural similarity between two chemical compounds, it is necessary to show some motivation that would have led one of ordinary skill in the art to select and then modify the original known compound to achieve the claimed compound.⁸² No such showing—or indeed, *any showing*—is required for an incremental pharmaceutical innovation to be presumed ineligible for patenting under Section 3(d), once it is determined that the innovation fits within one of the categories set forth in that section. Moreover, contrary to the theory advanced by proponents of Section 3(d), there are important dissimilarities

between the circumstances under which a patent applicant may rebut the presumption of obviousness under the US rule and the circumstances under which an incremental pharmaceutical innovation can qualify for patent under Section 3(d).⁸³ Under the US rule, an applicant may rebut a finding of *prima facie* obviousness by demonstrating that the claimed compound exhibits unexpected properties. Such properties can include, for example, better stability in high humidity or properties relating to the convenience of administration or use by patients—properties that would not contribute to therapeutic efficacy and would not, therefore, be a basis for patent eligibility under Section 3(d).⁸⁴ Unlike the “significantly enhanced efficacy” requirement of Section 3(d), there is no requirement under the US rule that unexpected results be of greater significance than the known or expected properties to overcome obviousness.

In the UK, a patent applicant can overcome a charge of obviousness by demonstrating an unexpected benefit that could not have been reasonably predicted.⁸⁵ Similarly, in the EU, an “unexpected technical effect” is an indication of an inventive step and thus of non-obviousness.⁸⁶ Like the US rule, these formulations are not limited to therapeutic effects.

The above analysis suggests that it is inaccurate to think of Section 3(d) merely as stating a standard of obviousness. Perhaps more importantly, the analysis also underscores the point that Section 3(d) bars inventions that may otherwise meet the requirements of patentability and thus are truly inventive.

An alternative suggestion short of reforming Section 3(d) is to include persons having backgrounds in pharmacology, rather than just pharma chemistry, in the patent examination process to aid examiners in their assessment of the efficacy arising from a particular incremental innovation. Proponents of this strategy argue that this would help ensure that incremental innovations that do in fact result in significant enhancements of therapeutic efficacy obtain patent protection.⁸⁷ While such a proposal may go some way to addressing problems associated with having patent examiners, who may not have the necessary background or training, assess therapeutic efficacy, it does not address the more fundamental problem that a substantial number of valuable and beneficial pharmaceutical innovations are not entitled to patent protection because of the categorical bar posed by Section 3(d).

In order to encourage incremental pharmaceutical innovations and realize the benefits of such innovation in India, the barrier against patent eligibility for such innovations should be removed from the Patents Act altogether. Removing Section 3(d) would allow all incremental innovations, including pharmaceutical innovations, to undergo examination and be treated in the same manner regardless of industry or field of technology. As a result of such a reform, patent applications directed to incremental pharmaceutical innovations would be assessed under the same standards of patentability and patent eligibility as are applicable to all other types of innovation. This would encourage innovation by Indian pharmaceutical companies, promote the incremental development of drug products of benefit to Indian patients, and bring India’s patent laws in line with the rest of the world. In addition, it would spur additional foreign direct investment in India as non-Indian pharmaceutical companies increasingly look to India as

an ideal location for clinical trials, due to low costs and a large, “therapy naïve” patient population, and increasingly look to partner with Indian pharmaceutical companies on drug development projects that expand the innovative capacities of Indian pharmaceutical companies.

Removing the restriction on the patenting of incremental pharmaceutical innovations need not result in the consequences feared by the proponents of Section 3(d)—an increase in patent evergreening, an increase in drug prices or a reduction in access to medicine by Indian patients. First, as the Mashelkar Committee found in its report on issues surrounding incremental pharmaceutical innovation, the problem of patent evergreening can be addressed adequately through rigorous application of the requirements of novelty and nonobviousness. Attempts to circumvent patent expiration on a drug product by seeking to extend patent coverage based on non-novel, trivial or otherwise obvious modifications or uses of a product should be prevented by a robust application of the requirements that a claimed invention be novel and non-obvious in order to be patentable. This is how patent evergreening is addressed in other jurisdictions, which have no analog to Section 3(d), and following international practice will only help Indian industry. Addressing patent evergreening through the rules of novelty and nonobviousness, as opposed to Section 3(d), ensures that truly inventive incremental innovations are rewarded and encouraged, while non-inventive modifications or uses are barred.

The problem of patent evergreening must also be viewed in context. When the term of a patent expires, the subject matter claimed therein is available for the public to use. Accordingly, if a

company obtains a patent on a new form of a known compound, that need not prevent the public from manufacturing, using or selling the compound in its original form once the earlier patent has expired. Thus, a patent on an incremental pharmaceutical innovation does not bar a generic company from selling a generic version of the original drug product once the patent covering that product has expired.

Second, removal of Section 3(d) from the Patents Act will not lead to an increase in drug prices or a decrease in access to medicine in India. As discussed above, incremental pharmaceutical innovation may in fact *increase* price competition by increasing the number of different drugs that exist within a given class, thereby contributing to an overall reduction in drug prices, especially in a competitive market such as India’s. Removing Section 3(d) may thus increase price competition. Moreover, as noted, patents on incremental pharmaceutical innovations do not prevent generic versions of the earlier product. The availability of generic competition on relatively close substitutes would provide an important constraint on the price of products based on later incremental innovations. Other aspects of Indian law also help constrain price and safeguard access to medicine. India’s competition laws address monopolistic and other practices that can affect drug prices or access to medicine. Finally, pursuant to the Drug Price Control Order of 1995, the National Pharmaceutical Pricing Authority sets ceilings on the prices of essential medicines.⁸⁸ These features of India’s economic and healthcare policy provide a more effective method of addressing concerns relating to the price of and access to medicine than Section 3(d).

CONCLUSION

This is a pivotal period in the history of Indian innovation. India stands poised to become a leading hub of global innovation, and Indian pharmaceutical companies are at the center of this process. Providing the right incentives for incremental pharmaceutical innovation can move India forward on this path and encourage the development of drug products that meet the needs of Indian patients. Reforming Section 3(d) to encourage and protect incremental pharmaceutical innovation would create such incentives and help India become a true powerhouse of innovation.

ENDNOTES

- ¹ UNLEASHING INDIA'S INNOVATION: TOWARDS SUSTAINABLE AND INCLUSIVE GROWTH 1 (Mark A. Dutz ed., 2007).
- ² *Id.* at xv.
- ³ KNOWLEDGE COMMISSION OF INDIA, INNOVATION IN INDIA iv (2007).
- ⁴ UNLEASHING INDIA'S INNOVATION, *supra* note 1, at 50-51.
- ⁵ *Id.* at 51.
- ⁶ Two examples of new compounds developed and patented by Indian companies are the novel anti-malarial drug Arterolane, developed by Ranbaxy, and the anti-diabetic drug Balaglitazone, developed by Dr. Reddy's.
- ⁷ See discussion *infra* at 5.
- ⁸ See discussion *infra*. at 5.
- ⁹ See discussion *infra*. at 6.
- ¹⁰ While some nations, for example, Pakistan, prohibit the patenting of secondary uses of known substances, India excludes from patent eligibility both new uses and new forms of known pharmaceutical substances – and thus potentially the entire range of beneficial incremental pharmaceutical innovations.
- ¹¹ NATIONAL RESEARCH COUNCIL, PROSPECTUS FOR NATIONAL KNOWLEDGE ASSESSMENT(1995) at 10.
- ¹² J. Cohen et al., The role of follow-on drugs and indications on the WHO Essential Drug List, 31 JOURNAL OF CLINICAL PHARMACY AND THERAPEUTICS 6,(2006).
- ¹³ World Health Organization, Essential Medicines, www.who.int/medicines/services/essmedicines_def/en (last visited Feb. 2, 2009).
- ¹⁴ See Albert Wertheimer et al., Too Many Drugs? The Clinical and Economic Value of Incremental Innovations, in 14 INVESTING IN HEALTH: THE SOCIAL AND ECONOMIC BENEFITS OF Healthcare INNOVATION 77-118 (Irina Farquhar et al. eds., 2001).
- ¹⁵ See WIPO Secretariat, Follow -On Innovation and Intellectual Property 8-9, www.wipo.int/patentscope/en/lifesciences/pdf/who_wipo.pdf (last visited Feb. 2, 2009).
- ¹⁶ *Id.* at 13-14.
- ¹⁷ Wertheimer, *supra* note 14, at 90-91.
- ¹⁸ See Shamnad Basheer, Limiting the Patentability of Pharmaceutical Inventions and Micro-organisms: A TRIPS Compatibility Review n.151 (November 2005) (on file with the Intellectual Property Institute, Oxford, UK).
- ¹⁹ Example provided during interviews with key stakeholders.
- ²⁰ See Albert Wertheimer & Thomas Santella, "Pharmacoevolution: the advantages of incremental innovation," IPN Working Papers on Intellectual Property, Innovation and Health, International Policy Network (2005), at 6-10.
- ²¹ Joseph DiMasi & Cherie Paquette, "The Economics of Follow-On Drug Research and Development: Trends in Entry Rates and the Timing of Development," Pharmacoeconomics (2004): 22 Supl. 2, at 8-9; see also National Institute for Healthcare Management Research and Educations Foundation, Changing Patterns of Pharmaceutical Innovation (May 2002) ("NIHCM Study"), at 7-10.
- ²² DiMasi & Paquette (2004), *supra* n. 21, at 8.
- ²³ Wertheimer & Santella (2005), *supra* n. 20, at 8.
- ²⁴ *Id.*
- ²⁵ Williams, J. W. Jr., Trivedi, M., Chiquette, E., Aguilar, C., Cornell, J.E. & Bedgett, R. et al. Treatment of Depression: Newer Pharmacotherapies. Publication No. 99–E014. Agency for Healthcare Policy and Research, US Department of Health and Human Services, Rockville, 1999.
- ²⁶ Evans, WE, and McLeod, HL, "Pharmacogenomics — Drug disposition, drug targets, and side-effects," New England J. of Medicine (2003); 348:538-549.
- ²⁷ DiMasi & Paquette (2004), *supra* n. 22, at 11; Wertheimer & Levy at 80-81.
- ²⁸ Wetheimer et al. (2001), *supra* n.17, at 81.
- ²⁹ *Id.* at 100-11.
- ³⁰ See, e.g., J. A. DiMasi and H. G. Grabowski, "The Cost of Biopharmaceutical R&D: Is Biotech Different?" Managerial and Decision Economics 28 (2007): 469-479; Mathukumalli Vidyasagar, "Cutting Drug Discovery Costs on the Subcontinent," The Scientist (2004), 18(20):54.
- ³¹ See Joseph DiMasi et al., "The Price of Innovation: New Estimates of Drug Development Costs," Journal of Health Economics 22 (2003) 151-185.
- ³² NIHCM Study, *supra* note 21, at 7-10.
- ³³ Data provided during interviews with key stakeholders.
- ³⁴ NIHCM Study, *supra* note 21, at 10-11.
- ³⁵ See H. Kettler & A. Towse, Public private partnerships for research and development: medicines and vaccines for diseases of poverty, Office of Health Economics, London (2002).
- ³⁶ DiMasi & Paquette (2004), *supra* n. 21, at 11.
- ³⁷ *Id.*
- ³⁸ For example, one study of the costs associated with absenteeism and diminished worker productivity resulting from seasonal hay fever found that the US economy lost on average between US\$2.4 billion and US\$4.6 billion per year because of the sedating effects of antihistamine medications. The incremental development of non-sedating antihistamines thus can be expected to reduce the costs associated with employee absenteeism due to seasonal hay fever. See Wetheimer et al. (2001), *supra* n.17.
- ³⁹ See DiMasi & Paquette (2004), *supra* n. 21 at 12; see also Joseph DiMasi, Price Trends for Prescription Pharmaceuticals: 1995-1999, <http://aspe.hhs.gov/health/Reports/Drug-papers/dimassi/dimasi-final.htm> (last visited Feb. 2, 2009).
- ⁴⁰ OFFICE OF HEALTH ECONOMICS CONSULTING, THE MANY FACES OF INNOVATION 26 (February 18, 2005), <http://www.ohe.org/lib/liDownload/48/Many%20faces.pdf?CFID=58055&CFTOKEN=32477601> (last visited Feb. 2, 2009).
- ⁴¹ See MCKINSEY & COMPANY, INDIA PHARMA 2015: UNLOCKING THE POTENTIALS OF THE INDIAN PHARMACEUTICALS MARKET 10, www.mckinsey.com/locations/india/mckinseyonindia/pdf/India_Pharma_2015.pdf (last visited Feb. 2, 2009). See also *id.* at 24 (noting that "incremental innovations through fixed-dose combinations" will be important to the growth of India's pharmaceutical market).
- ⁴² In India, D.G. Shah, Secretary-General of the Indian Pharmaceutical Alliance, has been a prominent exponent of this view in connection with the debate over Section 3(d) of the Patents Act. See, e.g., "Is India's Patent System Too Liberal In Practice?" THE ECONOMIC TIMES, January 9, 2009.
- ⁴³ Joseph A. DiMasi et al., The Price of Innovation: New Estimates of Drug Development Costs, 22 J. of Health Econ. 151, 173 (2003).
- ⁴⁴ See R.G. Frank, "New Estimates of Drug Development Costs," 22 J. Health Econ. 325-30 (2003).
- ⁴⁵ T. Mason, "R&D Productivity: How Should It Be Measured? A Perspective Based On Fundamental Principles," Presentation to Drug Information Association, Annual Meeting, Washington, D.C. (June 15, 2004).
- ⁴⁶ D.K. Nauriyal, "TRIPS-compliant New Patents Act and Indian Pharmaceutical Sector: Directions in Strategy and R&D," Indian Journal of Economics and Business (Sept. 2006), at 2.
- ⁴⁷ *Id.*
- ⁴⁸ J. Lanjouw, Patents, Price Controls, and Access to New Drugs: How Policy Affects Global Market Entry, NBER Working Paper 11321 (2005), at 26.
- ⁴⁹ WTO Trade Policy Review: India, WT/TPR/G/182 (2007), at 86.
- ⁵⁰ EvaluateServe Research, "Patenting Trends in India: Facts and Research," April 2008 (on file). The top ten domestic filers of patent applications in India as of 2007 included CSIR (which ranked number one), Ranbaxy, Dr. Reddy's Orchid Chemicals & Pharmaceuticals, Cadila Healthcare, and Cipla.
- ⁵¹ Katherine C. Linton & Nicholas Corrado, "A 'Calibrated Approach': Pharmaceutical FDI and the Evolution of Indian Patent Law," United States International Trade Commission J. of Int'l Commerce and Econ. 2 (August 2007), http://www.usitc.gov/journal/07_Pharm_FDI_Indian_Patent_Law.pdf (last visited Feb. 2, 2009).

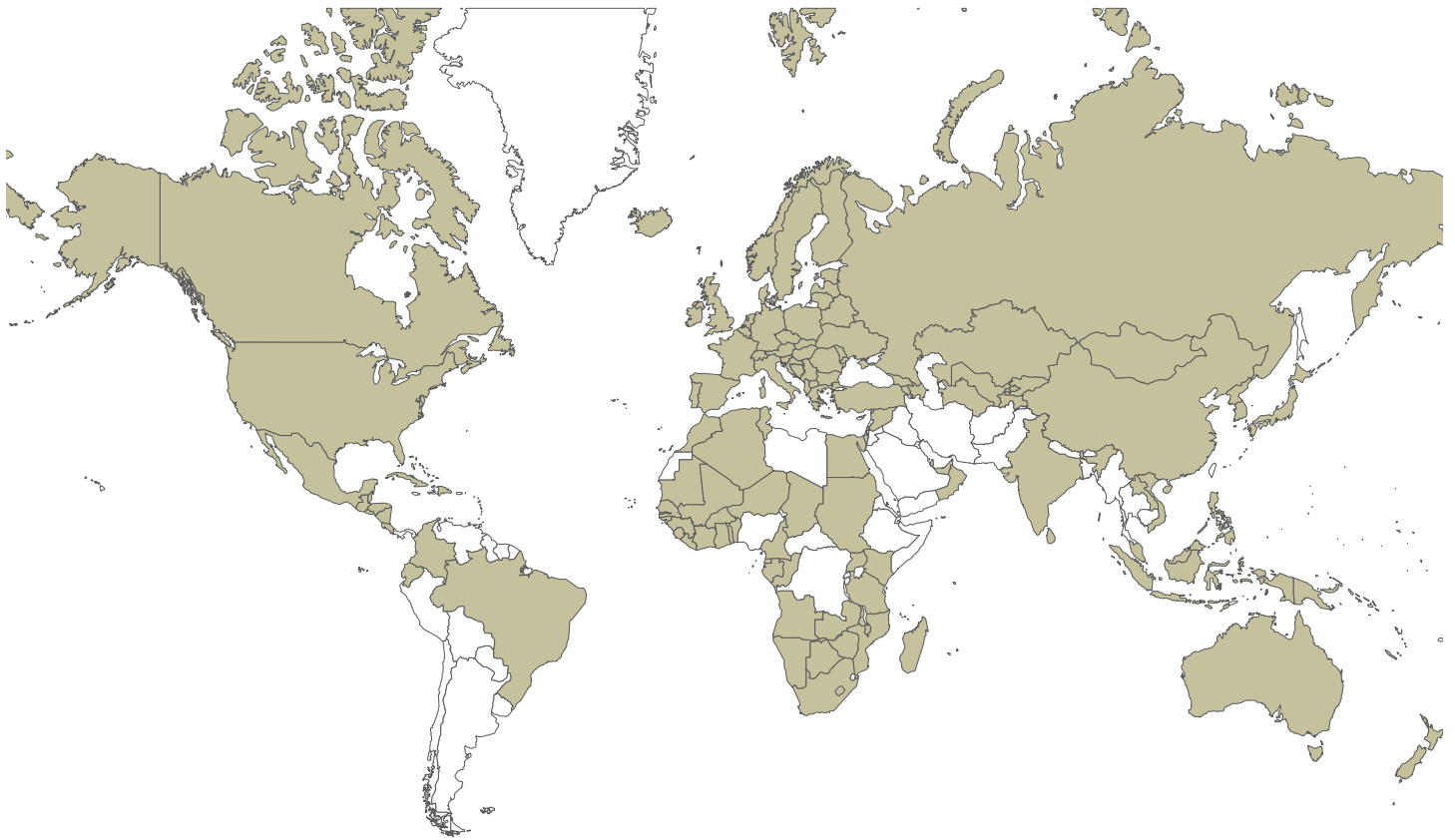
ENDNOTES CONT.

- ⁵² *Id.*
- ⁵³ Patents Act, § 3(d).
- ⁵⁴ *See* India Patents Act, § 3.
- ⁵⁵ Patents Act § 3(d).
- ⁵⁶ *Id.*
- ⁵⁷ Transcript of Parliamentary Debate, March 22, 2005.
- ⁵⁸ *Id.*
- ⁵⁹ *See* Janice M. Mueller, “The Tiger Awakens: The Tumultuous Transformation Of India’s Patent System And The Rise Of Indian Pharmaceutical Innovation,” 68 U. Pitt. L. Rev. 491 (2007) for a review of the political history of the 2005 patent law amendments.
- ⁶⁰ *Id.*
- ⁶¹ *See* Affidavit of Ranjna Mehta Dutt dated May 17, 2006, submitted on behalf of Novartis in *Novartis AG v. Union of India, et al.*, High Court of Judicature at Madras (Special Original Jurisdiction) W.P.No. 24759 of 2006.
- ⁶² *See* the High Court’s June 8, 2007 decision in *AG v. Union of India, et al.*, High Court of Judicature at Madras (Special Original Jurisdiction) W.P.No. 24759 and 24760 of 2006.
- ⁶³ *Boehringer Ingelheim Pharmaceutical v. Indian Network for People Living with HIV/AIDS & Positive Women’s Network*, Indian Patent Office, Application no. 2845/DEL/1998 (19th June, 2008). *See* also the discussion in Shamnad Basheer & T. Prashant Reddy, “The ‘Efficacy’ of Indian Patent Law: Ironing Out the Creases in Section 3(d),” 5 *SCRIPTed* 2 (2008) at 248. Section 3(d) was also at issue in a case in which the Delhi High Court denied an injunction that would have prevented Cipla from marketing a generic version of Roche’s anticancer drug Tarcerva. Cipla challenged Roche’s patent on several grounds including that it was a derivative of a known compound and thus not patentable under Section 3(d). In denying the request for an injunction, the court noted that Roche had not submitted data regarding the comparative efficacy of its drug over existing drug during patent examination and had not therefore shown significantly enhanced efficacy as required under Section 3(d). On appeal, the High Court affirmed the decision noting, *inter alia*, that the patentee had failed to demonstrate enhanced efficacy in support of its original application. In neither decision did the High Court analyze the meaning of “efficacy.” *See F. Hoffman-LaRoche Ltd. v. Cipla Ltd.*, High Court of Delhi at New Delhi, FAO (OS) 188/2008 (Apr. 24, 2009).
- ⁶⁴ *See* In the Matter of an Application for Patent No. 799/CHE/2004 filed on 12 August, 2004 (March 30, 2009).
- ⁶⁵ EU Directive 2004/27/EC, Art. 10(2)(b).
- ⁶⁶ Patents Act, § 39(1)(a). In addition, under sub-section 39(1)(b), a person resident in India may not file a patent application outside India if the invention is relevant to certain defense purposes and the Controller of Patents has restricted publication of information relating to the invention.
- ⁶⁷ As noted above, while some countries prohibit the patenting of secondary uses of known substances, in 2005 India was unique in restricting the patent eligibility of the full range of incremental pharmaceutical innovations, including new forms of known substances.
- ⁶⁸ International Chamber of Commerce, The Importance of Incremental Innovation for Development, Submission to the World Health Organization’s Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH) (May 7, 2005).
- ⁶⁹ *Id.*
- ⁷⁰ *See, e.g.*, R. Aoki & T. Saiki, “Implications of Product Patents – Lessons From Japan, Working Paper (April 2005).
- ⁷¹ *See, e.g.*, US 6,916,941; CA 2291134; AU 1989036295.
- ⁷² *See, e.g.*, EP 0347066.
- ⁷³ *Id.* at 23.
- ⁷⁴ *Id.* at 24.
- ⁷⁵ *Id.* at 40.
- ⁷⁶ *Id.* at 12.
- ⁷⁷ *Id.* The Mashelkar Committee Report was originally published in December 2006. A revised version of the Report was published in March 2009.
- ⁷⁸ *See, e.g.*, Janice M. Mueller, “Taking TRIPS to India – Novartis, Patent Law, and Access to Medicine,” 356 *New England J. of Med.* 541 (2007), <http://content.nejm.org/cgi/content/full/356/6/541> (last visited Feb. 2, 2009).
- ⁷⁹ *See, e.g.*, US Patent and Trademark Office Manual of Patent Examining Procedure § 2144.09 (8th ed.).
- ⁸⁰ *See, e.g.*, *In re Chupp*, 816 F.2d 643, 645-46 (Fed. Cir. 1987) (“evidence of unobvious or unexpected advantageous properties may rebut a prima facie case of obviousness based on structural similarities”) (citing *In re Papesch*, 315 F.2d 381 (CCPA 1963)).
- ⁸¹ No need to patent small changes, *FRONTLINE*, March 10-23, 2007 (interview with Dilip G. Shah).
- ⁸² *See Eisai Co. Ltd. v. Dr. Reddy’s Labs., Ltd.*, 533 F.3d 1353, 1356-57 (Fed. Cir. 2008); *see also KSR Int’l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007).
- ⁸³ *See Basheer & Reddy* (2008), *supra* note 63; *see also Basheer* (2005), *supra* n. 18.
- ⁸⁴ On the other hand, to be eligible for a patent under Section 3(d), it is not necessary that the enhanced efficacy be surprising or unexpected. Accordingly, Section 3(d) in fact potentially permits the issuance of a patent that would be barred as obvious under the US rule.
- ⁸⁵ *See Schering-Plough v. Norbrook* [2005] EWHC 2532; *see also Katherine A. Helm*, *The Battle Over Global Drug Markets: Enforcement of Pharmaceutical Patents in the United States, Europe and Japan*, 4 *J. of Intel. Prop. L. & Prac.* 39 (2009).
- ⁸⁶ EUROPEAN PATENT OFFICE, *GUIDELINES FOR EXAMINATION IN THE EUROPEAN PATENT OFFICE* 11.9.3 (December 2007).
- ⁸⁷ Based on interviews with interested stakeholders.
- ⁸⁸ *See* Drugs (Prices Control) Order 1995 ¶ 9.

APPENDIX

A Sample of Patent Applications Directed To Incremental Pharmaceutical Innovations Submitted By Indian Pharmaceutical Companies

Designated States



■ Country Designations in WIPO

A Sample of Patent Applications Directed To Incremental Pharmaceutical Innovations Submitted By Indian Pharmaceutical Companies

Wipo#/Date Of Application	Company	Title	Description
WO/2006/087629; Date of Application: 24.08.2006	Aurobindo Pharma Limited	Rapidly disintegrating composition of olanzapine.	<p>This patent describes a new combination of olanzapine, a drug used in the treatment of schizophrenia.</p> <p>In this patent, olanzapine is combined with a lubricating agent, a filler, and an agent that makes the drug rapidly disintegrate in the mouth of the patient.</p> <p>The claimed benefit is the ease of administration because this rapidly dissolving form can be administered without water—an advantage in patients with difficulties in swallowing and uncooperative patients.</p>
WO/2006/109175; Date of Application: 19.10.2006	Aurobindo Pharma Limited	Solid dosage form of an antidiabetic drug.	<p>This patent describes a combination of glyburide in a specific particle size with specific excipients to improve its dissolution in water. The patent also describes a process for making the combination.</p> <p>Glyburide, a drug used in the treatment of diabetes, is poorly soluble in water. The claimed benefit is the improved dissolution, and subsequent absorption, because of the specified combination.</p>
WO/2006/123243; Date of Application: 23.11.2006	Aurobindo Pharma Limited	Pharmaceutical dosage forms comprising escitalopram in form of granules.	<p>This patent describes escitalopram of a specific particle size produced by a granulation technique. Further, the patent claims a formulation combining these granules with specified excipients to improve dissolution of the drug.</p> <p>Escitalopram, commonly used in the treatment of depression and anxiety, is poorly soluble in water. The present patent claims that the proposed formulation confers a benefit by ameliorating the solubility problems of the drug.</p>
WO/2006/048894; Date of Application: 11.05.2006	Morepen Laboratories Limited	Novel crystalline forms of atorvastatin in calcium and processes for preparing them.	<p>This patent describes a polymorph of atorvastatin, a member of a class of drugs known as statins that are used extensively in the treatment of cholesterol.</p> <p>The patent claims that the new polymorphs described offer the benefits of higher purity and stability which facilitates storage of the drug and improves yield during its production.</p>
WO/2006/082598; Date of Application: 10.08.2006	Natco Pharm.	Novel crystalline forms of rizatriptan benzoate.	<p>The patent describes three novel crystalline forms of rizatriptan, a drug used in the treatment of migraine.</p> <p>The described forms are stable, reproducible, and suitable for pharmaceutical preparations. The patent also describes the process for manufacturing the same.</p>

Wipo#/Date Of Application	Company	Title	Description
WO/2006/103551; Date of Application: 05.10.2006	Ranbaxy Laboratories Limited	Controlled Release Formulations of Oxycodone.	<p>The patent describes a combination of oxycodone with a polymer that controls the release of the drug.</p> <p>Oxycodone is a well-known opioid analgesic and extended release formulations confer therapeutic benefits by providing prolonged pain-relief.</p> <p>This patent claims that the formulation described provides a means for producing an extended release formulation in a cost effective manner that is also easy to manufacture on commercial scale.</p>
WO/2006/046105; Date of Application: 04.05.2006	Ranbaxy Laboratories Limited	Oxcarbazepine dosage forms.	<p>The patent describes a formulation combining oxcarbazepine of a specified particle size with suitable excipients to produce both solid and liquid formulations suitable for oral administration.</p> <p>Oxcarbazepine, widely used in the treatment of epilepsy, is poorly soluble in water. The claimed patent describes a formulation that can conveniently administer a stable dose of the drug to the patient.</p>
WO/2007/029096; Date of Application: 15.03.2007	Ranbaxy Laboratories Limited	Novel polymorphic forms of clopidogrel hydrochloride.	<p>The patent describes a novel polymorph of clopidogrel hydrochloride, a drug that inhibits the formation of blood clots and is used in the treatment of strokes and heart-attacks.</p>
WO/2009/004592; Date of Application: 08.01.2009	Wockhardt Research Center	Vancomycin compositions.	<p>The patent describes a formulation of vancomycin in hard gelatin capsules for oral administration.</p> <p>Vancomycin is an antibiotic used in the treatment of serious infections.</p> <p>The benefits claimed include ease of handling and cost savings because the formulation described is cheap to produce compared to other dosage forms available.</p>

ABOUT US

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