ADAPTIVE INNOVATION, INTELLECTUAL PROPERTY AND THE PUBLIC INTEREST: HOW PATENT EXTENSION LEADS TO MORE, BETTER AND SAFER MEDICINES
Dear Reader

Two famous scientists — one a famous naturalist, Charles Darwin, and the other a brilliant economist, Alfred Marshall — both expressed a similar concept in terms of a Latin phrase, “Natura non facit saltum” — i.e., generally “nature does nothing in leaps”. In other words, nature, change — and innovation — reflect incremental movements in the normal course of events. This also happens in the course of pharmaceutical and vaccine progress. Change will often occur in molecules that may seem trivial, but they bring about tremendous changes in benefits to patients. For example, an improved formulation of an existing drug has resulted in a new indication that saves patients’ eyesight. In another case, adaptation of an existing drug to improve access to AIDS treatment has greatly increased the ability to save the lives of AIDS patients.

To appreciate better the application of what Darwin and Marshall long ago perceived, as it pertains to pharmaceutical innovation, IFPMA is publishing this paper, Adaptive Innovation, Intellectual Property and the Public Interest: How Patent Extension Leads to More, Better and Safer Medicines. It uses concrete examples to illustrate the importance of incremental innovation in improving public health, through the adaptation of existing products to meet new medical needs or to provide better treatment conditions for patients.

Such adaptive innovation depends on the protection and encouragement provided by the patent system. As the renowned management expert Peter Drucker noted, the patent system itself evolved significantly to bring about an incentive system that both promotes innovation and diffuses knowledge widely:

“Great Britain between 1750 and 1800 shifted from patents as monopolies to enrich royal favorites to patents granted to encourage the application of knowledge to tools, products and processes, and in order to reward inventors, provided they published their inventions. This not only triggered a century of feverish mechanical invention in Britain; it put an end to craft mystery and secretiveness.”

Without patent incentives, useful innovative adaptations would not take place and the public health benefits from such innovation would be lost. Five case studies illustrate the challenges faced in
improving existing products and how incremental innovation has made significant advances in health care and treatment possible for both communicable and non-communicable diseases. The innovations examined in this publication are:

- a single dose form of Zithromax®, an antibiotic that fights bacterial infections;
- a more efficient synthesis process for Neurontin®, a drug used for the treatment of neuro-psychiatric disorders.
- an extended release form of Procardia®, a drug for angina and high blood pressure,
- a novel approach to overcoming formulation stability problems with Agenerase™, a protease inhibitor used to treat HIV,
- a more tolerable version of Effexor®, an unprecedented antidepressant that works by selectively inhibiting the neuronal reuptake of serotonin and norepinephrine.

Efforts made to improve these products were substantial and important, as are the benefits to patients needing these improved products, and the process of the evolution of therapeutic compounds informs policymakers of the critical importance of the innovative processes of Darwin’s and Marshall’s observations as they apply to the life-enhancing science and art of pharmaceutical innovation.

I would like to thank Mr. William Looney of Pfizer for writing this paper and Messrs. David Rosenberg of GlaxoSmithKline, Douglas Hawkins of Wyeth, as well as Peter Corr and Peter Richardson of Pfizer for their important contributions to the text.

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1 Darwin referred to this principle as a “canon in natural history” in his *Origin of Species* and Marshall used this phrase as a header to the introduction to his *Principles of Economics*.
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It is a woman in Morocco who can see, not simply because scientists developed the antibiotic Zithromax, but because they went on to create the complicated mechanism that allows patients with blinding trachoma to take it in a single, easy-to-take dose that delivers a year’s worth of cure.

It is an epileptic spared seizures — or an elderly man or woman released from the agonizing pain of shingles — not simply because scientists developed Neurontin, but because they managed to find a novel way to manufacture it safely, for the intended indications, and in large amounts.

It is a patient free from the stabbing pain of angina, not just because researchers developed calcium channel blockers, but because they took the next step: finding a way to lengthen the potency and therapeutic benefits of these drugs in the human system, in extended release tablets.

It is a person living with AIDS in Uganda, surviving for years with a disease that has killed thirty million people in sub-Saharan Africa, not just because of the discovery of the HIV protease inhibitor Agenerase, but because teams of researchers found a way to surmount the low solubility of the manufactured compound that made it impossible to take orally, in capsule form.

And it is a victim of depression who can now control the symptoms of her illness, not only because pharmaceutical researchers discovered Effexor, a novel selective serotonin reuptake inhibitor, but also because they developed a new extended-release formulation that allows once-daily dosing, thereby
easing patient compliance and reducing severe side effects such as nausea and vomiting.

Each of these patients was helped by the system of patent protection that provides the inventor with the incentive to overcome the many barriers that loom before a promising medical advance can reach the real world. A world where the patient lies waiting for a new indication to attack a stubborn disease, for a more convenient dose that aids compliance, or for a better manufacturing process to ensure cost-effective production at high volumes and stability in storage.

It is a system that seems paradoxical to some. Can protecting incentives for a few inventors really protect the rest of us from the shifting, fast-adapting patterns of disease? In fact, protecting inventors has led to a stream of innovations that has lengthened the average life span by more than a decade for both men and women since World War II, while adding to the quality of that extra measure of life by making it largely free of the debilitating diseases that once afflicted millions.

It certainly helped these patients.

But the key point here is that these patients did not benefit from the ways that the patent system protects the inventor of a new drug. Instead, the patent system helped inventors achieve other, equally important breakthroughs: a new indication for an existing drug or a process improvement that either ensured a patient would benefit from a broader mode of treatment or would be better able to take and safely metabolize a complex medicine – more conveniently and often at lower cost.

To some analysts, patent protection for such refinements seems frivolous or trivial. They argue that it allows the R&D-based pharmaceutical industry to focus substantial resources on developing “marginal” improvements to existing therapies. They allege that because companies mainly seek to extend the commercial life of current products, the patient does not benefit from a true medical advance. According to this view, the current patent system encourages this strategy by allowing companies to claim patent protection for a host of trivial or minor changes – often shortly before the original patent expires. By extending the period of exclusivity, opponents say, companies prevent commercial rivals from entering the market at lower prices. The result is less generic competition, limited access to medicines for the poor
and a diversion of resources away from research that addresses the disease burden of neglected populations in developing countries.

Some who do not fully understand the innovation process have claimed that the main output of the big drug companies is “me-too” drugs: minor variations of highly profitable pharmaceuticals already on the market. Such critics allege that there is often little reason to think that competing drugs in the same therapeutic class have significant differences, since follow-on drugs are rarely compared against each other at equivalent doses in clinical trials.

In fact, no drug company sets out deliberately to develop a follow-on drug. Innovative companies working in the same therapeutic area compete to be the first to market to treat that condition. Normally, just one company can win that race and the medicines produced by runner-up companies become labeled “me too” by default, although they may actually have been developed in parallel with or even earlier than the first drug to market.

Such criticism of incremental innovation is prompted by a narrow vision of the R&D pharmaceutical industry as both imitative and anti-competitive: that any patent obtained beyond the patent on the original compound itself is “frivolous” because it is motivated solely by commercial reasons, rather than a commitment to innovation to benefit patients.

The truth is quite different. In fact, the patent system provides an essential guarantee that inventors will be rewarded for the risks they take during a process that averages more than a decade and consumes enormous financial resources. But in return they must transform “proof of concept” into a safe and effective medicine.

Why can’t trivial refinements to a product win a patent that can in turn be used to restrain competition? Because the patent system has stringent requirements that prevent someone from obtaining patent protection for something that is not new. Patent law requires that patent holders prove that their inventions are both novel and “non-obvious.” Patent law defines such an invention as one which a person with basic skills in the art could not normally derive from prior art, and is thus representative of an “inventive step.” In practical terms, this means that applicants must prove that the invention they seek to patent has new, improved or unexpected therapeutic effects or properties compared to what is known.
In addition, multiple patents relating to a single product sometimes result over time because significant hurdles were encountered in the product's development that, if not overcome, would have prevented its manufacture or its safe and effective use. Even the most innovative new compound will fail the test of the market if its pharmacokinetic properties prove unstable, if the medicinal content degrades in the human system or cannot be safely stored on the shelf, or if it cannot be manufactured in standardized acceptable quantities, at reasonable cost. These and other “inventive steps” that drive the long journey from laboratory to patient are critical to ensuring that a medicine is approved for the intended indication, with minimal risk to the patient population, and at a cost that the market will bear.

As profiled in a series of concrete examples contained in this paper, an invention can range from manufacturing improvements or modifications to changes in inert or active ingredients. None of these are “trivial” if the end result is a product approved by governments and accepted by patients.

Inventions that assist in overcoming these hurdles are legitimately patentable – from both a patent law and societal benefit perspective. Without them, the product would never have emerged from the registration process intact. Are such facilitating inventions “frivolous” or “trivial?” Not to patients who take the medicine which would not have otherwise been available.

Another point is that a patent covering an improvement to an existing patented product does not bar generic competition against this existing product once the patents protecting that product have expired. For example, if a company develops a once-a-day dose for a product originally prescribed twice daily and patents the new formulation, generic competition is still possible against the original, assuming the patent on the original drug has expired. The only patent protected version will be the new formulation. The market will then decide if the once-a-day benefit is worth a premium over cheaper generic versions of the original product.

The bottom line is simple and unequivocal: multiple patents do not prevent the advent of generic versions of patent-expired products. A product cannot be “double-patented.” A new patent covering an improvement to an existing product protects only the new improved version, such as the once-a-day dosing formulation cited in the example above. Both versions can be on
the market; competition is then between the off-patent original product and the patented new version.

Moreover, others can develop and market further formulations or once-a-day versions, provided they are different from those covered by the new patent. Only products that offer useful advantages over now off-patent products will be accepted by patients and the medical community. The patent system provides this incentive to “invent around” and thus encourages innovation and effectively precludes the original patentee from extending his exclusive position by making merely trivial changes.

In fact, in our industry, any new product must demonstrate distinct value to the patient and payer communities or it will not be accepted. Physicians, payers or patients do not respond to a new product simply on the basis of its patent status; the level of engagement is far more complex, with assessment of therapeutic benefit driving acceptance by the customer base.

To say that a company can dictate the timing of a patent or series of patents so as to extend a monopoly is simply contrary to the nature of science and the reality of invention. The realization of an inventive step is inherently unpredictable – if it were not, then research and development would not be so resource-intensive and time-consuming, especially in the pharmaceutical sector. Statistics demonstrate that the first compound in a new class that is patented and submitted for registration is only rarely the first to be actually approved for marketing to consumers. In fact, many compounds are abandoned at some point during the lengthy clinical trial process and never reach patients at all.
INNOVATION: IT’S IN THE EYE OF THE BEHOLDER

There are many types of innovation in pharmaceutical R&D. This question was specifically acknowledged by the European Union [EU] Working Group on Pharmaceuticals and Public Health in its March 2000 report³ to the EU High Level Committee on Health:

“Innovation in pharmaceuticals encompasses many different options, going from the development of a completely new medicine for the treatment of a disease otherwise incurable, to modifications of known pharmaceutical formulations to improve benefits for the patients, such as a less invasive administration route or a simpler administration schedule.”

The concept of an incremental improvement to an existing pharmaceutical [or other] product that can be deemed an innovation worthy of a patent is also recognized and codified in US patent law, as follows:

“Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.” [35 USC sec.101]

This concept is not limited to the US: it is incorporated in the patent regimes of all countries that have implemented systems that are compliant with the 1994 WTO Agreement on Trade Related Intellectual Property Rights [TRIPS].

Several US government agencies have examined the issue of alleged frivolous patent filing. Of note is the fact that their findings do not support allegations of widespread abuse. A study by the Food and Drug Administration [FDA] found that of the 8,259 generic applications filed in the US between 1984 and January 2001, 94 percent, or 7,781 applications raised no patent issues and involved no patent litigation. Launches of the vast majority of generic products were unimpeded by any patent.

The same outcome can be found in a more recent Federal Trade Commission study⁴. The study looked at whether there was abuse by patent holders

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⁴ See FTC Generic Drug Entry Prior To Patent Expiration: An FTC Study (July 2002).
through the filing of frivolous patent infringement suits as a way to delay the advent of generic competition. Out of the more than 8,000 generic drug applications filed with FDA since 1984, the Commission identified only eight cases of possible concern. In effect, it found that about one-tenth of one percent [0.1%] of all generic filings generated possible frivolous patent suits.

Conversely, it can be said that the generic industry itself has a strong incentive for such activity, particularly given the supportive protections offered to the industry under the US Hatch-Waxman Act. Essentially, when a generic company files a generic application (ANDA) with a Paragraph IV Certification (non-infringement or invalid patent), the company is in a minimal risk, maximum reward position. If it wins the case, it gets on the market quickly. If it loses, it owes no damages.

PUTTING THEORY INTO PRACTICE: FIVE CASE STUDIES

The following five cases illustrate the value of incremental innovation and the role that patents play in providing a wide range of useful product developments that in turn depend on the time, effort and resources expended by the innovator. These cases demonstrate that patents, far from being a defensive weapon to limit competition among low value products, actually drive technological progress by encouraging and enabling the investment needed to overcome the many hurdles in the long, expensive process of developing a novel idea into a tangible product. And it is often at the latter stages where the real hurdles – involving fundamental issues like ease of manufacturing or safe product formulation – begin to appear.

The five cases involve four research-based pharmaceutical companies and span the past 25 years. They have a common theme, in that in each case the company concerned:

• started with a compound that was already patented from a material standpoint (i.e. the chemical form of the compound was protected)
• faced barriers limiting the compound’s benefit for patients, and
• required further innovative biology/chemistry advances to overcome substantial scientific and manufacturing challenges
The first and most recent case looks at the development of a single dose form of Zithromax, an antibiotic that fights bacterial infections. The second case focuses on the development of a more efficient synthesis process for Neurontin, a drug used for the treatment of neuro-psychiatric disorders. The third examines the development of an extended release form of Procardia, a drug for angina and high blood pressure, while the fourth reviews a novel approach to overcoming formulation stability problems for Agenerase, a protease inhibitor used to treat HIV. The fifth example explores the challenges of finding a more tolerable version of Effexor, an unprecedented antidepressant that works by selectively inhibiting the neuronal reuptake of serotonin and norepinephrine.

**Case Study 1: Zithromax SR [azithromycin]**

**Context**

Compliance with (or adherence to) the treatment regimen is a critical issue for patients taking antibiotics to fight infections. Patients who do not complete their prescribed course of therapy are only partially treating the infecting bacteria. This may lead to treatment failure and/or the development of antibiotic resistance. Patient compliance can be a particularly important issue in resource-poor settings where lack of medical infrastructure can mean low capability to monitor patient progress. Consumer research shows that only about 60 per cent of patients adhere to antibiotic therapy.

Compliance can be greatly enhanced by simplifying the treatment regimen such as decreasing the number of tablets taken per day, lessening the overall treatment duration, or by both. While compliance is a problem in the developed world, the problem is even greater in the developing world, where healthcare infrastructure is poor. An ideal therapy would require taking the medicine orally, just once, at the time of the visit with the physician. However, many drug therapies require taking a large number of doses over as many as fourteen days.
Challenges

Zithromax, an antibiotic used to fight infections, was an improvement over other therapies when it first appeared on the US market because it required a shortened treatment duration of only five days; however, gastrointestinal (GI) side effects prohibited Zithromax from being taken as a one-time dose for most infections.

About a decade or so ago, Pfizer scientists started a project to turn Zithromax into a single dose form: Zithromax SR. The team faced a series of challenges.

Solution

GI Side Effects: The first step was to understand how Zithromax produced side effects when given in a single dose. Through a series of small scale human studies that spanned two years, Pfizer scientists identified the issue: high concentrations in the upper GI tract produced the side effects, however high concentrations in the lower GI tract did not. The question remained: could they find a way for the drug to bypass the upper GI tract?

Creating a formulation: Pfizer scientists knew that a liquid suspension was the only viable form because a solid form would require patients to take too many pills. During the five year development of the liquid that could deliver the drug to the lower the GI tract, many issues were encountered that required experience and creativity to solve. Two illustrative examples related to how the drug was included in the liquid suspension:

• the scientists created ‘beads’ to carry the drug in the liquid using an innovative composition designed to slow the drug’s release until it reached the lower GI tract;

• They also optimized the size of the ‘beads’ to produce an easily suspended and swallowed liquid suspension, while maintaining the capacity to slowly release the drug.

Optimizing the formulation: Once the liquid suspension was established, it was necessary to determine whether it would actually reduce GI side effects. Before committing to a large Phase III trial, Pfizer performed a Phase II trial in 2001 which failed to show reduced side effects. After a reformulation, Pfizer performed a second Phase II trial in 2002 that was successful.
Testing Efficacy: From 2002-2004, the extended release suspension was successfully tested in over 3,000 patients in a Phase III trial.

This 13-year research and development process took significant effort, resources, resilience and ingenuity, but led to a single dose suspension that met medical and commercial requirements. Over 90 employee years, accompanied by large financial investments, were applied to meet this goal. The key achievement of increasing the dose delivered in the single dose to 2g, compared to the previous normal dose of 1.5g delivered over three to five days, served to raise efficacy and further reduce the chance of resistance developing – i.e. “a dead bug cannot mutate.” The innovative suspension formulation was patented along with the original compound – and was essential to the product’s eventual success. The resulting innovative product has substantial therapeutic value and will have a significant impact in the fight against antibiotic resistance in both the developing and developed world. *Zithromax* is now also used as a treatment for trachoma, the leading cause of preventable blindness in the developing world.

**Case Study 2: Neurontin [gabapentin]**

**Context**

*Neurontin* is now an important option for the treatment for seizure disorders [epilepsy] and is the leading treatment worldwide for neuropathic pain that can occur after shingles. However, even though safety and therapeutic value were established in Phase I and Phase II clinical trials, the drug was nearly abandoned, due to challenges in scaling up the production process to commercial volumes.

**Challenges**

Warner Lambert faced three key scale-up issues:

- **A very costly process:** Making the drug required extreme physical and chemical conditions, e.g. high temperatures and concentrated acidic solutions. These conditions were very expensive to create and, on a large-scale, would result in significant amounts of environmental waste.
• **Limited quantity of drug:** The process was only capable of producing the small quantities of drug adequate for pre-clinical, Phase I and Phase II clinical trials. Regardless of the investment required, it was fundamentally unclear whether the science could be scaled-up to higher volumes.

• **Potential quality issues:** At a small scale, the quality of each individual tablet was high, but if significant increases in scale were achieved, scientists faced further challenges to limit impurities and maintain stability of the drug.

In 1988, ten scientists were given two years to design a more efficient process to reliably produce large quantities of *Neurontin*. If they could not, the project would be abandoned.

**Solution**

The nature of invention is essentially unpredictable and many unique problems need to be solved through the process. Two examples of challenges faced by the team that required innovations in chemistry were:

- The need to develop an alternative key reagent when the global supply of the reagent used previously was no longer available due to political tensions.

- Designing a reaction that had never been achieved before. This involved academic research, benchmarking across other industries, and developing complex statistical analysis methods to identify the unique conditions and ingredients necessary to produce the desired reaction.

By 1989, the team had invented a novel and efficient process that required less extreme conditions, resulted in little environmental waste, and produced a purer form of *Neurontin* than the original process. Thereafter, another team of 10 scientists required 2 more years to scale up the new process to the point where it could supply market demand from large manufacturing plants.

This 40 employee-year effort to design a workable production process required significant resources and innovation and was critical to bring this therapy to patients. In recognition of the team's achievements in intellectual property, the new production process was patented in 1992.
Case Study 3: Procardia XL

Context

Procardia belongs to a class of drugs known as calcium channel blockers (CCBs) and originally came to market in 1982 as a treatment for angina – chest pain associated with coronary heart disease. Today, a number of CCBs are approved for the treatment of high blood pressure (hypertension) and provide significantly greater therapeutic value than when Procardia first came to market. This advance was made possible by addressing issues with the way the original drug was released into the bloodstream.

Challenges

Although capable of relieving angina, the original formulation of Procardia had to be taken three times a day. This regimen was difficult from a patient compliance standpoint and led to large swings in blood levels with accompanying changes in blood pressure that prevented the drug from being completely effective.

Scientists at Pfizer hypothesized that if they could ensure more stable blood levels by creating an extended release form of Procardia, it would have significant potential to change the way the drug was used and benefit a whole new group of patients by treating high blood pressure much more effectively.

Solution

In 1982, Pfizer began a partnership to develop a proprietary extended release technology. Three key issues had to be addressed:

- **Adapting the technology to Procardia**: Since the partner’s technology had never been used with a therapeutic, it had to be re-designed specifically for Procardia. This required a two year collaboration between the company and Pfizer scientists to design a system to release Procardia at just the right rate to maintain constant blood levels.

- **Creating a mass production facility**: Two to three years were then spent developing the equipment to mass produce Procardia XL at a manufac-
turing site and another year to both build the equipment and gain FDA approval for the production facility.

- **Evaluating clinical activity**: Since this new technology had never reached patients before, the FDA had a number of questions about its reliability. Before *Procardia XL* could enter Phase II studies, Pfizer ran a wide array of safety studies to address FDA concerns. After answering all of their questions and running successful Phase II and III trials, *Procardia XL* showed remarkably consistent blood levels over a 24 hour period with fewer side effects than *Procardia*. *Procardia XL* was subsequently approved for both angina and high blood pressure indications.

This seven-year process produced a drug that altered the way an entire class of therapeutics was used in patient care. Consistent blood levels of CCBs opened a paradigm of treatment that more than tripled the patient population that could benefit from this therapy. This significant effort and innovation to develop *Procardia XL* resulted in a patent for the drug formulation.

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**Case Study 4: Agenerase**

**Context**

Formulation stability and bioavailability are of key importance in the development of a new drug. If it cannot be formulated in a form which can be stored for a suitable length of time, the product will not pass the strict requirements for regulatory approval and thus a potentially valuable new treatment for a disease may never reach the patient. If it cannot be formulated in a manner in which the quantity of the drug needed can be delivered in a dosage form that is acceptable to the patient, then patient compliance problems will arise.

**Challenges**

*Agenerase* is an HIV protease inhibitor. At the time of its development, protease inhibitors were a relatively new class of drugs for treating HIV. With the HIV virus capable of developing resistance to existing therapies, the medical world was very keen for new therapeutic options for patients.
However, amprenavir, the active substance in Agenerase, has very low solubility and “wettability” [i.e. the extent to which a solid is wetted by a liquid, measured by the force of adhesion between the two] and was thus very difficult to formulate. In addition, poor solubility resulted in low bioavailability of the powder in capsule and tablet formulations. Bioavailability is a particularly important consideration in the HIV arena since patients generally take a range of treatments and thus have a relatively high pill burden. New treatments with low bioavailability would add to this burden and thus patient compliance would become harder to achieve.

Solution

Scientists at Glaxo SmithKline identified that the bioavailability of amprenavir in conventional capsule or tablet form was low partly due to its high molecular weight [506 g/mol], poor water solubility [0.04 mg/ml, pH 7.5], and high dose [1,200 mg twice a day]. They discovered that vitamin E-TPGS [a form of vitamin E that is water soluble, as opposed to other forms which are fat soluble] enhanced the absorption flux of amprenavir and improved its bioavailability. Given the fact that it is relatively safe to use, vitamin E-TPGS was determined to be of high importance to the development of a stable and acceptably bioavailable Agenerase formulation.

This novel and inventive solution to the formulation problem, which enabled the product to gain marketing approval and become a viable treatment, was recognized by the granting of patent protection. Indeed, without this solution, there would have been no way to ensure the pill was effective for its intended patient population.

Case Study 5: Effexor [venlafaxine]

Context

In the 1980s, Wyeth researchers developed venlafaxine as an unprecedented antidepressant that works by selectively inhibiting the neuronal reuptake of serotonin and norepinephrine, two naturally occurring neurotransmitters that have been implicated in depression and other mental disorders. Wyeth scientists recognized venlafaxine’s promise as an important antidepressant medication and pressed forward with its development. Wyeth
launched venlafaxine for the treatment of depression in the United States in early 1994 under the trade name *Effexor*. The medicine was originally launched in an immediate release dosage form.

**Challenges**

Although effective, venlafaxine did not attain widespread use, primarily because many patients who used it experienced nausea and vomiting. Many patients who could have benefited from this unique drug were deprived of an effective therapy because of these side effects.

**Solution**

Wyeth researchers worked to develop an extended-release formulation that could provide adequate blood plasma levels of venlafaxine, such that it could be taken once a day. This was a significant advance that was sufficiently inventive to warrant a patent for, when development started, it was not known if a once-a-day formulation would be therapeutically effective. Not only did Wyeth's research result in a formulation that could be administered once daily while maintaining efficacy, thereby making it more convenient for patients and improving compliance, but it also unexpectedly reduced side effects, such as nausea and emesis, as compared to the immediate release formulation. Venlafaxine is now widely prescribed because patients are able to adhere to the dosing regimen and tolerate therapeutic blood levels without lengthy and severe nausea.

The ability of patients to benefit from the power of venlafaxine is to a large extent attributable to the efforts of Wyeth's work on the extended release formulation. Had Wyeth stopped its research efforts after discovering venlafaxine and launching *Effexor*, the true potential of this drug would never have been realized.
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