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Issue Analysis

Pharmaceutical Evolution

The Advantages of Incremental Innovation in Drug Development

By Albert I. Wertheimer and Thomas M. Santella

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Executive Summary

Innovation is the lifeblood of the pharmaceutical industry. Over the last century, that industry has been responsible for thousands of new drugs, based on hundreds of thousands of smaller incremental innovations. The breakthrough "blockbuster" drugs taken by millions of patients today were not produced from thin air. Most represent the combined weight of seemingly small improvements achieved over time. The advantages of incremental improvements on existing drugs are paramount to overall increases in the quality of health care. As the pharmaceutical industry developed, classes of drugs—those with similar chemical composition and which treat similar conditions—have grown to provide physicians with the tools they need to treat diverse patient groups.

Still, critics have been highly condescending about what they call "Me-too" drugs—drugs within the same chemical class as one or more others already on the market—which they claim add little or no therapeutic value and are nothing more than an opportunity for pharmaceutical companies to fleece unsuspecting consumers. While some claim that there are too many similar drugs, and that pharmaceutical industry research and development could be more profitably directed toward developing entirely new classes of medicines, drugs based on incremental improvements generally represent advances in safety and efficacy. They also provide new formulations and dosing options that significantly increase patient compliance—both of which lead to improved health outcomes. From an economic standpoint, adding new drugs to a class of medicines also offers the possibility of lower drug prices as competition between manufacturers increases. Additionally, pharmaceutical companies depend on incremental innovations to provide the revenue that will support development of the riskier, capital- and research-intensive blockbuster drugs.

When critics refer to Me-too drugs, they do not mean exact generic copies of already existing drugs, or illegal counterfeits. Instead, Me-toos have a similar chemical composition to one or more others on the market, and have similar biological effects. But, in order to be approved, Me-too drugs must undergo the same extensive clinical testing as other new drugs to determine their safety and efficacy because they are *chemically* different. In addition, these differences, even if small, typically must represent a medical advancement—such as fewer side effects or improved efficacy for patient sub-populations—in order to attract a portion of the market away from the first approved drug in the class. Nevertheless, many drug industry critics have called for federal policies to inhibit the development and marketing of such incrementally improved medicines. But policies that curb incremental innovation will ultimately lead to a reduction in the overall quality of existing drug classes and could arrest the creation of truly novel drugs.

Research in any industry is a building process. Few scientists develop groundbreaking drugs from no prior research. Most work within, and respond to, existing knowledge—reading the same medical literature, and reacting

to new technological breakthroughs at the same time. It is not hard to imagine, therefore, that many different companies would be working on similar drugs. In fact, it is often the case that the only reason why one drug is called novel and another a Me-too analogue is the speed at which each moves through the regulatory process.

Like other technological and value-added industries, the pharmaceutical industry depends on small steps for the creation of blockbuster drugs, which often result from a long series of small innovations. It also depends on these steps for the creation of drugs that provide slight, incremental improvements on existing drugs—thereby adding to a drug class, increasing competition among drugs, and incentivizing further innovation. As the National Research Council has observed, "the cumulative effect of numerous minor incremental innovations can sometimes be more transforming and have more economic impact than a few radical innovations or 'technological breakthroughs'." The net effect of increasing the number of drugs through innovation leads to advances in safety, efficacy, selectivity, and utility of drugs within a specific class.

Importantly, providing physicians with a variety of prescription options within a given therapeutic class is paramount to the provision of optimal health care. This is especially true for some drug classes, such as those relating to the central nervous system, for which overall response rates can be as low as 50 percent. For unknown reasons, certain patients respond differently to different drugs within a single class. If physicians have many options at their disposal, they can calibrate their prescribing patterns to better address the needs of specific patients. The existence of multiple similar molecular agents also provides backup in situations where the novel drug in a class is found to have unacceptable side effects and is thus removed from the market. As patients come to depend on a particular class of drugs, it is essential to make sure that they do not lose access to needed medication as a result of regulatory action.

One of the most vehement criticisms made against Me-too drugs is that they siphon money away from research that could be devoted to the creation of novel breakthrough drugs. This assumption is incorrect for a host of reasons, the most important of which is the fact that the pharmaceutical industry depends on selling the products of incremental innovations to provide the revenue for research and development of breakthrough drugs. Additionally, while it is unrealistic to presume that every incremental innovation leads to cost savings, the sum of all drug innovations can result in cost savings by reducing *overall* treatment costs, shortening or obviating hospital stays, increasing worker productivity and reducing absenteeism, and lowering drug costs through increased competition among manufacturers.

Ideally, every new drug would represent an unprecedented breakthrough and lead to the creation of a completely novel treatment. This, however, is not the reality of the pharmaceutical industry, or of any other development-based industry. Creating drugs based on incremental innovations provides pharmaceutical companies with a secure stream of revenue, which can be directed to higher-risk, potential blockbuster-yielding research. Policies aimed at reducing the industry's ability to obtain revenues from incremental innovations could be self-defeating, as those industries will then have less revenue to reinvest in R&D for new drugs. Put simply, limiting incremental drug innovation is analogous to limiting competition. The ultimate result could have devastating consequences for the future of the pharmaceutical industry and for the millions of patients who depend on it.

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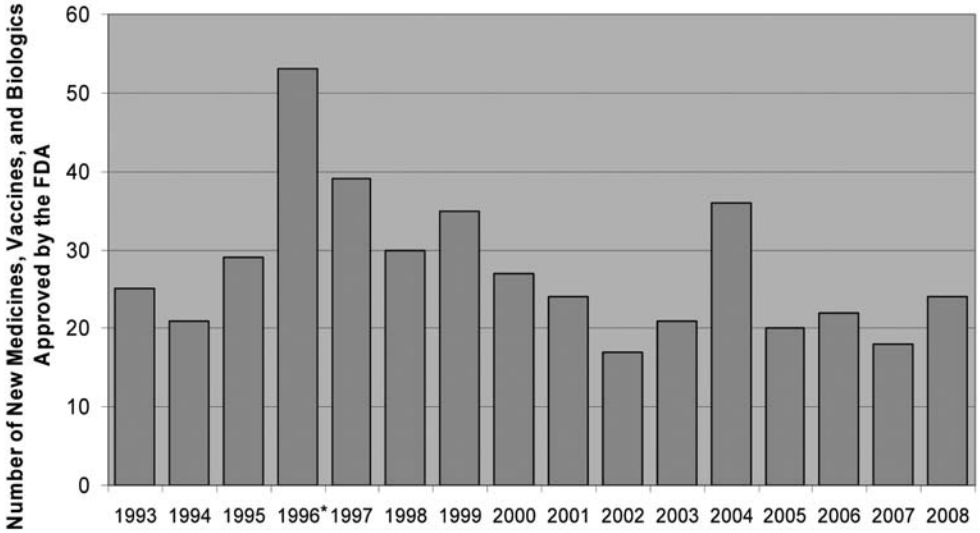
Introduction

Throughout human history, innovation has been the mainstay of progress. It has fueled economies, created new industries, and provided humanity with innumerable advantages and new opportunities. Over the last century, the pharmaceutical industry has developed from localized patent medicine makers to the expansive, research-based multinational entities of today. Over this long course, the pharmaceutical industry has been responsible for thousands of new drugs, based on hundreds of thousands of smaller incremental innovations. The breakthrough "blockbuster" drugs taken by millions of patients today were not produced from thin air. Most represent the combined weight of seemingly small improvements achieved over time.

Still, critics have been highly condescending about what they call "Me-too" drugs—drugs within the same chemical class as one or more others already on the market—which they claim add little or no therapeutic value and are nothing more than an opportunity for pharmaceutical companies to fleece unsuspecting consumers.[1] But the pharmaceutical industry's uniquely large research and development activities represent a process, even a gamble, not a calculated recycling of currently existing pharmaceutical products. If the latter were the case, we would expect to find very few, if any, new drugs over time. Instead, the pharmaceutical industry conducts clinical trials on hundreds of experimental medicines every year, and has brought an average of 27.5 new medicines to market every year over the last 15 years (see Figure 1). Put simply, innovation is the pharmaceutical industry's lifeblood.

Figure 1. Phamaceutical Research Company Scientists Earned FDA Approval for an Average of 32 Medicines a Year Over the Past Decade*



** A larger than average number of approvals in 1996 reflects the implementation of the Prescription Drug User Fee Act (PDUFA).*
Source: U.S. Food and Drug Administration, January 2005, and the Wall Street Journal, 2009.

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Nevertheless, many drug industry critics have called for federal policies to inhibit the development and marketing of such incrementally improved medicines. Marcia Angell, a former editor-in-chief of *The New England Journal of Medicine*, suggests that, in order to receive federal Food and Drug Administration (FDA) approval, Me-too drugs should be tested not just against placebo, but also in comparative trials against other drugs in the same class in order to show clinical superiority.[2] Former U.S. Senator (and one-time Secretary of Health and Human Services nominee) Tom Daschle has called for federal policies to rein in health care costs by limiting access to, or reimbursement for, treatments that do not provide sufficient "bang for the buck."[3] But policies that curb incremental innovation will ultimately lead to a reduction in the overall quality of existing drug classes and could arrest the creation of truly novel drugs.

This paper discusses the importance of incremental innovation within the pharmaceutical industry. Our review of the clinical pharmacology literature over the last two decades reveals that new versions of existing drugs are often characterized by improvements in therapeutic and adverse effects profiles, metabolism, dosing schedules, and ease of administration. We also found that the availability of a broad range of drugs provided physicians with the necessary tools to treat widely diverse patient groups, supplying them with secondary and tertiary

options when initial treatments failed. Additionally, we analyze the cost and benefits of having multiple drugs competing within the same market. Lastly, we examine the potential adverse effects of policies aimed at limiting incremental innovations.

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What Is a Me-too Drug?

To understand the difference between drug innovation and mere replication, it is crucial to explain what critics mean when they refer to a "Me-too" drug. While the term has been applied loosely to any new drug added to an already existing class, it generally refers to drugs that have a similar molecular structure, which are used to treat the same conditions (although we will show that this is not always the case). Before exploring the development and impact of drugs labeled as "Me-too," it is necessary to better define the term.

First, when critics refer to Me-toos, they do not mean exact copies of already existing drugs, which can be either legal generic copies or counterfeits. In actuality, patent laws prohibit drug manufacturers from copying and marketing already existing drug products until their patent expires. To be approved, new drugs must undergo an extended trial period designed to determine not only the drug's safety but also its efficacy. In other words, new drugs must be *chemically* different in order to be approved and marketed as new. Typically, these differences, even if small, must represent a medical advancement—such as fewer side effects or improved efficacy for patient sub-populations—in order to attract a portion of the market away from the first approved drug in the class.

Second, when critics use the term "Me-too," they are essentially casting aspersions on manufacturers' motivations, since labeling a drug as a Me-too implies that its manufacturer undertook no new research and is simply profiting from someone else's creation. While such motivations may not be wholly absent among industry players, it is rash to assume that this is all that lies behind the creation of new drugs. From an economic standpoint, it is fair to assume that all drug manufacturers, in investing in a new drug product, hope that it will become the next blockbuster drug. Even when working with an already existing drug product, manufacturers are likely searching for ways to improve the drug in such a significant way as to become the market leader in a specific class of drugs. No manufacturer wants to come in second place.

Third, writing off all new non-blockbuster drugs as mere Me-too products does not account for the reciprocity inherent in all research-based

industries. In today's globalized economy, drug research does not occur in a box. While manufacturers may be very secretive about their newest drugs, it is more likely that all manufacturers have at least some idea about what others are working on. Research in any industry is a building process. While few scientists develop groundbreaking drugs from no prior research, most work within, and react to, existing knowledge. Reading the same medical literature, and reacting to new technological breakthroughs at the same time, it is not hard to imagine that many different companies would be working on similar drugs. In fact, it is often the case that the only reason why one drug is called novel and another a Me-too analogue is the speed at which each moves through the regulatory process.

Research in any industry is a building process. While few scientists develop groundbreaking drugs from no prior research, most work within, and react to, existing knowledge.

Last, it is this type of competition, this back-and-forth development process, that spurs new breakthrough drugs. Most of the time, innovation does not lead to a novel drug but to a less well recognized addition to an existing drug class. It is these incremental additions which we will examine in greater detail. Before moving to that discussion however, we should first turn to one last important distinction regarding Me-toos.

Evergreening and Me-too Drugs Are not the Same

To understand the subtleties of incremental innovation, it is important to make clear the distinction between the marketing of new incremental drugs and "evergreening." Though the terms are often used interchangeably, evergreening refers to a tactic used by pharmaceutical companies to pre-empt their own patent expirations. Generally, and especially in the case of blockbuster drugs, generic companies are prepared to enter a particular market immediately after the innovator company's patent expires. For the innovator company, this translates into an average loss of approximately 40 percent of its market share to generic manufacturers within a fairly short period of time.[4]

In order to diminish the losses experienced when the patent expires, the innovator company may release an improved version of its drug prior to its patent expiration, thus preempting the release of generic versions of its blockbuster drug and possibly slowing the expected losses of market share and profits. While many criticize this tactic as an exploitation of a loophole in the patent system—as it is often accompanied by legal action targeted at slowing down generic activity—it should not be confused with incremental innovation. While some crossover may

exist, it is imperative to separate the constructive process of incremental innovation from transparent attempts to extend patent protection periods with minor modifications of little therapeutic advantage.

The Evolution of Pharmaceutical Therapies

Like the evolution of all species, technological advances tend to occur incrementally, one step at a time. As a result, progress is made over time, as many small steps add up to the proverbial giant leap. Like other technological and value-added industries, the pharmaceutical industry depends on these small steps for the creation of blockbuster drugs, as these drugs often stem from a large number of small innovations. It also depends on these steps for the creation of drugs that provide a slight improvement on existing drugs, thereby adding to a drug class, increasing competition among drugs, and creating a stimulus for further innovation. As the National Research Council has observed, "the cumulative effect of numerous minor incremental innovations can sometimes be more transforming and have more economic impact than a few radical innovations or 'technological breakthroughs'."[5] The net effect of increasing the number of drugs through innovation leads to advances in safety, efficacy, selectivity, and utility of drugs within a specific class.

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Expanding the Primary Therapeutic Unit

The conglomeration of drugs created through incremental innovation results in the expansion of drug classes. When a breakthrough occurs, a new class is created, thus laying the groundwork for even more innovative advances (see Figure 2). As a result of this cycle, the pharmacopoeia is characterized by many drug classes, each with its own group of molecularly similar drugs. But within any given class of drugs, each drug has its own unique therapeutic properties, which can have surprisingly differing results on patients. In order to meet the diverse needs of any patient group, it is much better to have many options—whereby the physician can match the patient with the best medicine—than only a single choice which may or may not be suitable for certain patients.

In order to be accepted within the class by the physicians who prescribe or by the insurers who pay for medical treatments, each new drug must also represent some price advantage or a cumulative improvement in efficacy, selectivity, reduced toxicity, or a combination of these factors. The end result is a class that is defined by the contributions of its many agents.

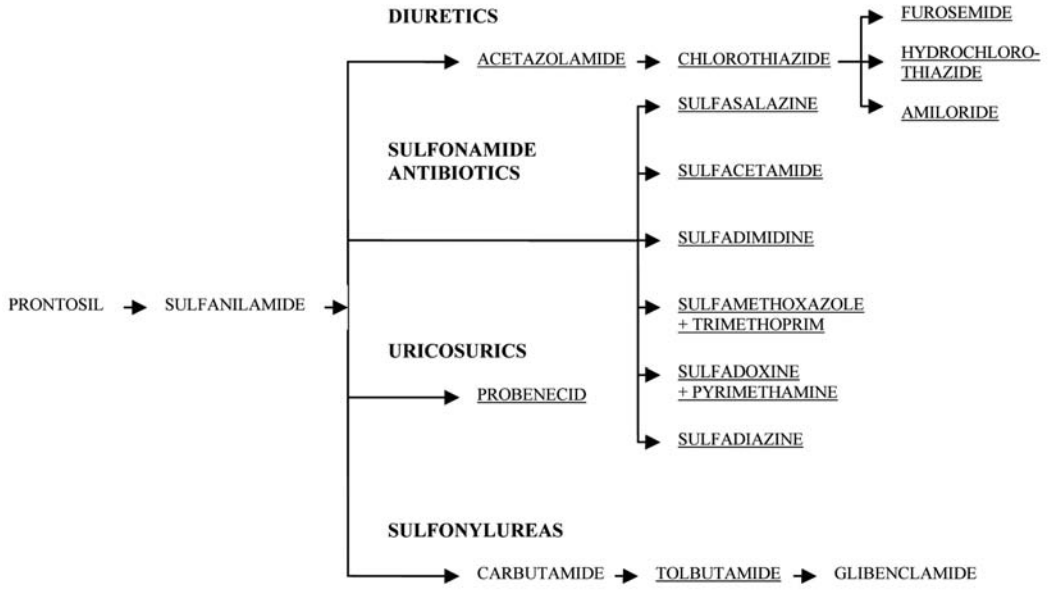
As patients come to depend on a particular class of drugs, it is essential to make sure that patients do not lose access to needed medication as a result of regulatory action.

The Importance of Alternatives

Providing physicians with a variety of prescribing options within a given therapeutic class is paramount to the provision of optimal health care. This is especially true for some drug classes, such as those relating to the central nervous system, for which overall response rates can be as low as 50 percent.[6] For unknown reasons, certain patients respond differently to different drugs within a single class. If physicians have many options at their disposal, they can calibrate their prescribing patterns to better address the needs of specific patients. Drug classes that exhibit high fluidity in overall response rates include selective seratonin re-uptake inhibitors (SSRIs) and non-steroidal anti-inflammatory agents (NSAIDs).[7]

In addition to providing doctors with an arsenal of therapeutic possibilities, the existence of multiple similar molecular agents provides backup in situations where the novel drug in a class is found to have unacceptable side effects and is thus removed from the market. As already discussed, drugs in any class typically represent improvements on the original drugs. As patients come to depend on a particular class of drugs, it is essential to make sure that patients do not lose access to needed medication as a result of regulatory action. There have been many cases in which the originator drug was removed from the market placing increased burden on the other drugs in its class. Examples include the antihistamines terfenadine and astemizole; the NSAIDs zomepirac, benoxaprofen and

Figure 2. The Evolutionary Drug Innovation Process



Example of how me-too research within a therapeutic drug class results in the discovery of other therapeutic classes and indications. Drugs underlined are those drugs included on the 1987 WHO essential drug list.

suprofen; and the fluoroquinolone antibiotic grepafloxacin—all removed as a result of clinical results showing infrequent but severe side effects.

It has certainly been the case in the past that most innovator drugs are replaced in time with better and more effective drugs. In 1999, for example, nearly all of the top-10 drugs prescribed in the United States were products of incremental innovation—Prilosec, Lipitor, Prozac, Prevecid, Zocor, Zoloft, Claritin, Paxil, Norvasc, and Augmentin.[8] Another study, conducted by Wastila et al. examined the World Health Organization's Essential Drug List and found that half of the drugs represented incremental improvements on older drugs.[9] These findings are significant because they show that for any given class of drugs, the original breakthrough drug does not always remain the most effective or best in the group.

In addition to the obvious benefits of medicine alternatives, there is one other factor that Me-too critics fail to grasp. Many developmental projects begin as blockbuster initiatives at the labs of different firms, and only later do the researchers realize other laboratories have been working independently on a drug development project in the same therapeutic category and even around a similar chemical entity. How rapidly the laboratory work and the pace of Phase 1, 2, and 3 clinical testing progress is not always predictable. Problems such as recruiting volunteers or delays at the centers conducting clinical trials make it difficult to determine in advance which is the "true" innovator product when all three files might be delivered to the FDA within a month of each other.

In addition, sometimes the same new drug, developed by different manufacturers, might obtain approval in different parts of the world at slightly different times. If product A is approved first in the United States while product B becomes the first approved in the European Union, which is the innovator and which is the Me-too? For this reason, and others, it is unfair to make accusations about so-called trivial modifications when that may

Sometimes the same new drug, developed by different manufacturers, might obtain approval in different parts of the world at slightly different times. If product A is approved first in the United States while product B becomes the first approved in the European Union, which is the innovator and which is the Me-too?

Table 1. Analysis of Me-Too Drugs on Essential Drug List

Year	*Analyzed Drugs**	*Number of Me-too Drugs*	*Percentage of Me-too Drugs*
1977	159	75	47.2
1979	171	78	45.6
1983	178	82	46.1
1985	187	83	44.4
1987	195	95	48.7

* Drugs and indications meeting criteria for inclusion
Source: Wastila, Linda J. J. Clin Res. Drug Dev. 3:105-115 (1989).

not have been the intention. In the previous example, both pharmaceutical manufacturers were hoping for a first-in-class blockbuster product.

Advances in Dose Delivery Systems and Dosage Forms

Over time, great strides have been made in the area of drug delivery systems and dosage forms. These are critical. Beyond the significant therapeutic value of a given drug, there exists a precarious network of factors affecting the drug's therapeutic impact. It is well known that a drug's rate of absorption plays a significant role in determining its therapeutic value. While fast absorption can cause increased adverse effects and may necessitate more frequent dosing, advanced delivery systems can provide molecules with staying power, prolonging their therapeutic effect.[10] Examples of advances in delivery systems and dosage forms include transdermal delivery, delayed-onset, extended release oral formulations, as well as the use of liposomes to reduce toxicity and polymers to sustain constant delivery rates.[11]

Extending the Usefulness of Breakthrough Drugs

Another area of innovation involves the use of new formulations to extend the uses of existing drugs. In many cases, this process allows a single molecule to be used effectively for several conditions. In other cases, reformulating leads to new essential drugs. One example is budesonide inhalation suspension, an inhaled corticosteroid for treating children with asthma—the active ingredient in the first available inhalers for children with asthma. In this case, the reformulation of an old drug led to a new and important medicine.[12] Table 2 shows additional examples of drugs that have been reformulated for new and extended uses.

Providing Variability to Meet Patients' Needs

While critics have concluded that incremental innovations do little more than produce more of the same to increase industry profits, an examination of the major classes of drugs yields a much different picture. The improvements made to the classes of antihistamines, beta blockers, and non-steroidal anti-inflammatory drugs provide good examples of the net effects of incremental innovation.

Antihistamines

First-generation antihistamines provided effective therapy but were characterized by a host of negative side effects, including anticholinergic

Table 2. New Formulations with Extended Uses

Drug	Original Indication	New Formulation	Extended Uses
Antibiotics	Parenteral use only	Oral preparations	Bowel preparation, hepatic coma Skin, eye, ear infections Cystic fibrosis
Corticosteroids	Steroid-responsive conditions	Topical forms Inhaled use	Same use with greater efficacy and safety Ulcerative colitis
Cromolyn sodium	Prophylaxis of asthma by aerosol Eye drops	Intravenous bolus injections Enemas	Hay fever Hay fever
Glyceryl trinitrate	Angina	Nasal insufflation	Greater efficacy
Heparin	Intravenous treatment for venous thrombosis	Transdermal patch	Prophylaxis of postoperative venous thrombosis
Medroxyprogesterone acetate	Endometriosis	Subcutaneous low-dose	Long-term contraception
Morphine	Pain	Depot injection	Prolonged action Regional analgesia
Pilocarpine	Glaucoma	Slow-release injection Epidural injection	Prolonged action
Vancomycin	Parenteral antibiotic	Oil-paste (Matrigel) capsules	Antibiotic-induced pseudomembranous colitis

Source: Snell, E, "Postmarketing Development of Medicines," Pharmacy International, 7(2), 33-37, 1986.

effects (interference with the involuntary movement of smooth muscles in the gastrointestinal tract, urinary tract, lungs, and elsewhere), penetration of the blood-brain barrier, and severe drowsiness. Additionally, the therapeutic effect of these drugs dissipated rapidly thus necessitating frequent dosing. Second-generation antihistamines, (including astemizole, loratadine, and cetirizine) constituted significant improvements on the originators. They significantly extended the therapeutic effect, reduced penetration of the blood-brain barrier, created no anticholinergic effects, and drastically reduced drowsiness. Third-generation antihistamines developed from the active metabolites of the second-generation drugs—such as fexofenadine (sold as Allegra), which is the primary active derivative of terfenadine (Seldane)—have led to even greater

Because no single beta blocker works well for all patients, it is necessary for physicians to have many options at their disposal.

therapeutic value with increased safety and efficacy profiles. As a result of this breakthrough, terfenadine was removed from the market once its manufacturer secured FDA approval for the safer fexofenadine.[13] Despite such an improvement in safety, these too could easily by disparaged as mere Me-too drugs.

Beta blockers

The development of beta blockers into a wide-ranging diverse class of drugs has allowed physicians to provide more individualized treatment. Because no single beta blocker works well for all patients, it is necessary for physicians to have many options at their disposal. After the introduction of propranolol, many new generations have advanced in selectivity and provided many diverse agents with vastly differencing therapeutic characteristics (including atenolol, bisoprolol, metroprolol, and betaxolol). These new drugs show differences in preserving renal blood flow, dosing schedule, changes in serum lipid levels, sympathomimetic activity (that is, producing effects similar to stimulation of the sympathetic nervous system, which is connected to the heart and blood vessels, sweat glands, etc.), central nervous system penetration, vasodilation, and effect on different racial groups. Often, matching a patient to the right beta blocker is a process of trial and error, as some products simply work for some patients better than others. Together, these many options provide an increased net therapeutic value.

As Table 3 shows, further research and development work beyond the original propranolol product resulted in at least eight new options for physicians, thus optimizing the therapeutic effectiveness of this therapeutic category for every type of patient. For example, subsequent products added valuable features not found with propranolol, such as preserving blood flow to and from the kidneys, reducing mortality after a heart attack, selectivity targeting the B1 receptor, and other benefits. Other less obvious improvements include tablets over capsules, where patients can take a half tablet to more precisely customize a dosage regimen, or liquids or chewable dosage forms for senior patients and others who cannot swallow solid dosage forms.

Non-Steroidal Anti-inflammatory Drugs

Evolution of the non-steroidal anti-inflammatory drug (NSAID) class once again shows that patients require a variety of drugs. While most of the currently available NSAIDs have similar safety and efficacy profiles,

Table 3. Advantages of Selected Beta Blockers

	Preserves blood flow to and from the kidneys	Reduces mortality after heart attack	Once daily dosing	No change in blood cholesterol levels	Selectively targets β_1 receptors	Equal effectiveness in blacks and whites	ISA[c]	Very low central nervous system penetration	Relaxes blood vessels resulting in improved blood flow
Acebutolol		♦			♦		♦		
Atenolol		♦			♦			♦	
Labetalol	♦			♦		♦			♦
Metoprolol		♦[a]	♦		♦				
Nadolol	♦	♦						♦	
Pindolol	♦			♦			♦		♦
Propranolol		♦[b]	♦						
Timolol			♦					♦	

[a] Once a day for hypertension.
[b] For controlled-release preparation only.
[c] Drug possesses "intrinsic sympathomimetic activity," which allows blockade of excess stimulation of heart by sympathetic nerves while maintaining adequate blood flow through the heart and peripheral blood vessels.

Source: Frishman, W, "Clinical differences between beta-adrenergic blocking agents: implications for therapeutic substitution," American Heart Journal, 113, 1190-1198, 1987.

patients still react differently to different drugs. Studies analyzing the prescription patterns of rheumotologists have shown that most of the available NSAIDs are prescribed. Additionally, patients typically switch medications over time, in many cases moving beyond two different drugs.[14,15,16]

In addition to the improvements made to antihistamines, beta blockers, and NSAIDs, numerous other classes have experienced similar gains from incremental innovation. Indeed, there have been drastic improvements in effects profiles of evolving calcium channel blockers.[17] Oral contraceptives have been continually improved to lessen harmful side effects and provide diverse treatment options.[18] Diabetes medications have drastically advanced, offering a wide variety of peak effect times, which allow physicians to better measure and adjust dosing.[19] And antipsychotics have developed to decrease cardiovascular effects.[20] While these are just a few of the classes whose development and improvement are the result of arduous incremental improvements made over many years, they are testament to the importance of supporting innovative endeavors.

Economic Implications

One of the most vehement criticisms made against Me-too drugs is that they siphon money away from research that could be devoted

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to the creation of novel breakthrough drugs. This assumption is incorrect for a host of reasons, the most important of which is the fact that the pharmaceutical industry depends on selling the products of incremental innovations to provide the revenue to invest in developing its breakthrough drugs. Additionally, while it is unrealistic to presume that every incremental innovation leads to cost savings, the sum of all drug innovations can result in cost savings in the following areas:

- Reduced *overall* treatment costs.
- Shortened or obviated hospital stays.
- Increased worker productivity and reduced absenteeism.
- Reduced drug costs from increased competition among manufacturers.

Reduced Treatment Costs

The cost of a new drug derives from a complex compromise between contending parties, which is beyond the scope of this paper. However, regardless of how prices for new drugs are determined, research indicates that the creation of new drugs in a class improves the overall treatment of the condition in question and can reduce overall costs through a combination of increased compliance, fewer hospital and physician visits, and increased worker productivity. Contributions to cardiovascular therapy and the addition of newer angiotensin converting enzyme (ACE) inhibitors provide clear examples of reduced overall costs resulting from incremental innovation.

- **Cardiovascular therapy**. Perhaps the largest influence on cardiovascular therapy over the last several decades has been the introduction of controlled-release (CR) formulations. The application of CR formulations to anti-hypertension drugs has resulted in improved efficacy, safety, and compliance results.[21] As a result of the introduction of CR formulations, nifedipine is now available in a one-a-day dosage form, and transdermal clonidine can now be given once a week, as compared to twice a day. Both of these cases have led to improved compliance, which has in turn decreased overall costs.

- **ACE Inhibitors**. A study conducted by Small et al., in 1997, analyzed and compared the costs of older treatments against those of newer treatments with ACE inhibitors. Utilizing a cohort of

6,000 elderly hypertension patients, it was found that the overall median cost per month for treatment with older drugs was $60, while for newer ACE inhibitor treatments it was $53. It was also found that newer agents correlated with greater compliance when compared to their predecessors—66 percent and 58 percent, respectively.[22]

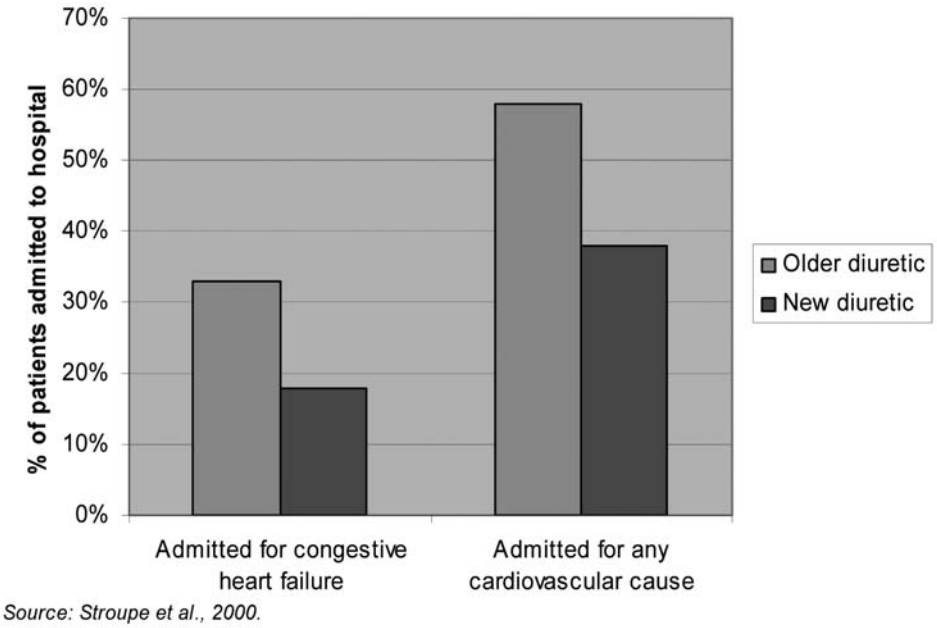
Reduced hospital costs

In many instances, the introduction of new drugs correlates directly with fewer hospital stays or physician visits. For example, a study conducted comparing the hospital costs associated with congestive heart failure (CHF) patients taking the original loop diuretic furosemide compared with those taking the newer torasemide found that the newer drug was correlated with reduced costs (see Figure 3). Specifically, those taking the newer torasemide experienced a 16-percent reduction in CHF-related admissions and a 20-percent reduction in general cardiac related admissions. Additionally, the study observed a net annual savings garnered from torasemide of $700,000 for CHF admissions and $1.3 million for cardiac events.[23]

Increasing productivity

Ultimately, when advances within a class of drugs alleviate debilitating side effects, the result is a quicker recovery period resulting in increased work capacity. The example of antihistamines exemplifies the correlation

Figure 3. New Diuretic Associated With Fewer Hopital Admissions



Source: Stroupe et al., 2000.

Promoting policies that aim to curb incremental innovation is analogous to advocating the creation of monopolies.

between incremental advances and increased productivity. Numerous studies have been undertaken to estimate the costs associated with absenteeism and diminished worker productivity resulting from seasonal hay fever. One study found that in the U.S. productivity losses ranged from $2.4 billion to $4.6 billion per year.[24] The researchers found that the main reason for these losses was the reduced productivity associated with the sedating affects of antihistamine medications. The advance and use of newer, non-sedating antihistamines has had a drastic effect on these figures, leaving workers relatively unaffected by their allergic rhinitis.[25]

Competition

In addition to improving the overall quality of care, incremental innovations also increase competition between drug manufacturers, thus lowering drug prices. This effect is not unique to the pharmaceutical industry—it is one of the guiding principles of open markets and free competition. Promoting policies that aim to curb incremental innovation is analogous to advocating the creation of monopolies. In the case of pharmaceuticals, in order for a drug to enter and become successful in an already established class, it must represent either significant therapeutic improvements or carry a lower price. A study conducted by DiMasi in 2000 showed that new drugs entering existing classes are often priced at a discount (see Table 4). Of the 20 drugs examined by DiMasi, 13 represented discounts of at least 5 percent.[26] When analyzing the market in this way, it seems that the problem of Me-too drugs may be not that there are too many but too few.

Policy Implications

The costs associated with bringing a new drug to market are extensive (see Figure 4). Often a new drug represents over a decade of research and development and millions upon million of dollars invested. Of these drugs, the vast majority result in a dead end, for which no revenue is ever obtained and no costs are ever recovered. Creating drugs based on incremental innovations provides an acceptable avenue for pharmaceutical companies to be better assured revenue, which can then be used to fuel higher-risk, potential blockbuster-yielding projects.

Policies aimed at reducing the industry's ability to obtain revenues from incremental innovations could be self-defeating, as those industries will then have less revenue to reinvest in R&D for new drugs. When viewing the pipelines of today's largest pharmaceutical companies, one

notices that only a small percentage of the new drugs produced could actually be considered blockbuster drugs. The reason for this may simply be that blockbuster drugs are developed at a much slower pace than those that are improvements on older drugs. Clearly, it is much easier to make an incremental improvement on an already existing product than it is to develop something completely novel. For this reason, much of the revenue obtained by the pharmaceutical industry comes from these incremental drugs. It is often this revenue that keeps the company in business. Therefore, policies that limit this form of revenue may ultimately lead to fewer blockbuster drugs.

Ideally, every new drug could represent an unprecedented breakthrough and lead to the creation of a completely novel drug. This, however, is not the reality of the pharmaceutical industry, or of any other development-based industry. For the pharmaceutical industry, novel drugs alone are not enough to support the expansive R&D costs. Based

Table 4. New Drugs in Existing Classes Tend to be Priced at a Discount (Adapted from DiMasi, 2000).

Subclass	Brand Name	Launch Month and Year	Discount Relative to Weighted Mean Price (%)	Discount Relative to Price Leader
ACE inhibitors	Univasc	May 1995	52.7	67.8
	Mavik	June 1996	30.4	53.2
ARBs	Diovan	February 1997	1.4	1.4
	Avapro	October 1997	-2.6	-2.6
	Atacand	October 1998	0.3	0.3
	Micardis	December 1998	0.7	0.7
CCBs	Sular	February 1996	37.7	67.9
	Posicor	July 1997	8.8	55.0
COX-2 inhibitors	Vioxx	May 1999	0	0
Macroslides	Dynabac	October 1995	42.6	49.0
Non-sedating antihistamines	Allegra	August 1996	14.1	15.0
PPIs	Prevacid	May 1995	10.1	10.1
	Aciphex	September 1999	4.9	6.7
Statis	Lipitor	January 1997	33.9	60.1
	Baycol	January 1998	29.5	43.1
SNRIs	Serzone	February 1995	9.7	9.7
SSRIs	Luvox	January 1995	8.1	12.7
	Celexa	August 1998	17.9	23.0
Third-generation cephalosporins	Cedax	February 1996	-7.4	20.0
	Omnicef	August 1998	-3.1	18.2

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; CCB = calcium channel blocker; COX-2 = cyclooxygenase-2; PPI = proton pump inhibitor; SNRI = serotonin norepinephine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

[a] A positive value indicates a lower price for the new entrant, while a negative value indicates a higher price.

Source: R.E. Small, S.B. Freeman-Arnold, J.R. Goode & M.A. Pyles, "Evaluation of the total cost of treating elderly hypertensive patients with ACE inhibitors: A comparison of older and newer agents," Pharmacotherapy, 17, 1011-1016, 1997.

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on the high-risk nature of their business, pharmaceutical companies strive to maintain a balance between research on highly innovative and potentially high-profit drugs and less risky incremental drugs that can guarantee revenue while still representing a medical advancement. In the end, policies limiting incremental innovation may disrupt the delicate balance between R&D and revenue maintenance. This is not to say that the pharmaceutical industry should not be subject to any regulation for safety. But policy makers should be aware of the significant difference between incremental drugs and mere copycat drugs as the future of drug innovation hangs in the balance.

Conclusion

The pharmaceutical industry, like every other industry in today's highly competitive and globalized economy, must find ways to reduce risks while maximizing profits—this is no secret. However, the pharmaceutical industry *is* unique in that it is an extraordinarily and unusually high-risk, high-profit industry. Opponents argue that limitations on incremental drug innovations will lead to increased investment and, in turn, a greater number of new blockbuster drugs. But when in our history has an industry been helped by reduced profits?

There is a trade-off here to be contended with: Would we rather have fewer pharmaceutical companies investing huge capital in high-risk projects that are more likely to fail than succeed or many pharmaceutical companies with diversified pipelines investing in safer incrementally innovative drugs that reduce risk, therefore providing the capital for investment in more risky endeavors? Clearly, the choice is between fewer companies with less overall innovation or more companies making continual and constant improvements on older drugs while still investing in blockbusters. If history is any guide to industrial success, competition drives innovation. Put simply, limiting incremental drug innovation is analogous to limiting competition. The ultimate result could have devastating consequences for the future of the pharmaceutical industry and for the millions of patients who depend on it.

Notes

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