

**Pharmacoevolution:**  
**the benefits of incremental innovation**



# Pharmacoevolution: the advantages of incremental innovation

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# Introduction

## Abstract

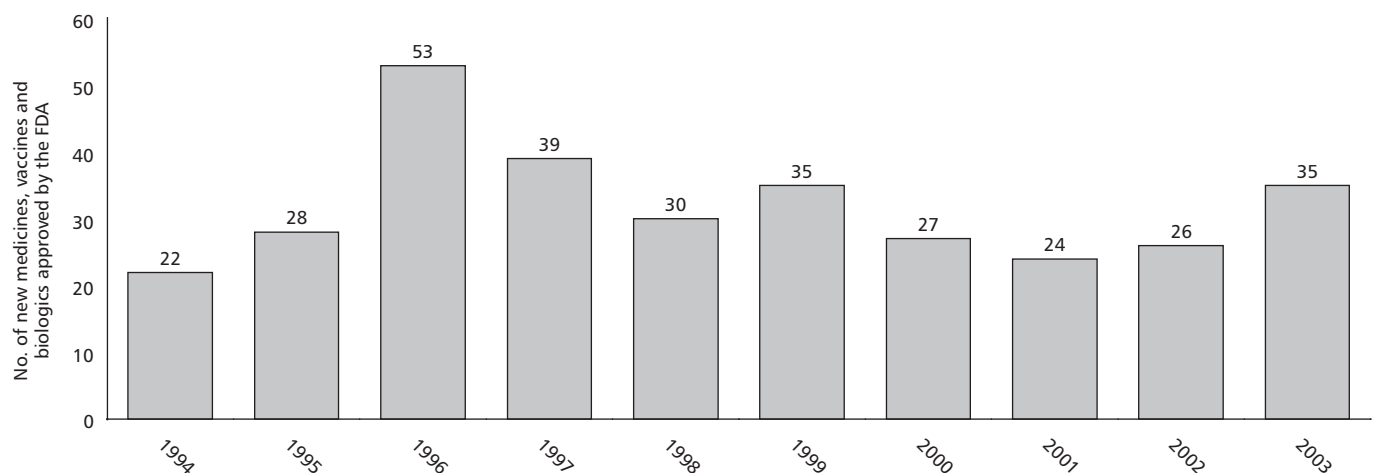
The advantages of incremental improvements on already existing drugs are paramount to overall increases in the quality of health care. As the pharmaceutical industry has developed, classes of drugs have expanded to provide physicians with the tools they need to treat diverse patient groups. While critics claim that there are too many similar drugs, drugs based on incremental improvements often represent advances in safety and efficacy, along with providing new formulations and dosing options that significantly increase patient compliance. From an economic standpoint, expanding drug classes represent the possibility of lower drug prices as competition between manufacturers is increased. Additionally, pharmaceutical companies

depend on incremental innovations to provide the revenue that will support the development of more risky “block-buster” drugs. Policies aimed at curbing incremental innovation will ultimately lead to a reduction in the overall quality of existing drug classes and may ultimately curb the creation of novel drugs.

## Introduction

Throughout human history innovation has been the mainstay of progress; it has fuelled economies, created new industries, and provided humanity with enumerable advantages and new opportunities. Over the last century, the pharmaceutical industry has developed from localised patent medicine maker to the expansive research-based multinational pharmaceutical entity of

Figure 1 **Pharmaceutical research company scientists earned FDA approval for an average of 32 new 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: US Food and Drug Administration, January 2004

today. And over this long course, the pharmaceutical industry has been responsible for thousands of new drugs, based on hundreds of thousands of smaller incremental innovations. It is worth pointing out that so-called “blockbuster” drugs taken by millions of patients today were not produced from thin air. But critics have been highly scathing towards what they refer to as “me-too” drugs – drugs that they claim are simple copies of already existing molecules. But the pharmaceutical industry’s uniquely large research and development side represents a process, even a gamble, not a calculated recycling of currently existing chemical entities. If this were the case, we would expect to find very few, if any, new drugs over time (see figure 1). This, as we know, has not been the reality. Why? Put simply, innovation is the life-blood of the pharmaceutical industry.

This paper discusses the reality of incremental innovations 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 analyse the cost benefits of having multiple drugs competing within the same market. Lastly, we postulate the potential adverse effects of policies aimed at limiting incremental innovations.

# Pharmacoevolution: the advantages of incremental innovation

## What is a “me-too”?

In understanding the difference between legitimate 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 labelled as “me-too”, it is necessary to define a bit more clearly what the term means.

First, it must be understood that when critics refer to “me-too’s”, they are not referring to exact copies of already existing drugs. These drugs are either legal generic copies or counterfeits. In actuality, patent laws prohibit drug manufacturers from copying and marketing already existing drug products, until the time that their patent expires. In order 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 represent a medical advancement, even if small, in order to be approved and marketed.

Secondly, it is important to understand that when critics use the term “me-too”, they are in essence casting aspersions on the motivations of the manufacturer. By this we mean to say that labelling a drug as a “me-too” implies that its manufacturer undertook no new research in its creation and is simply exploiting the market to increase profits. While we do not purport that these motivations are wholly absent from the industry’s mindset, we think it 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 “block-buster” drug. Even when working with an already existing drug product, manufacturers are likely searching for ways to improve the drug in such an extensive way as to become the market leader in a specific class of drugs. No manufacturer wants to come in second place.

Thirdly, writing off all new non-“block-busters” as mere “me-too” products does not account for the reciprocity inherent in all research-based industries. In today’s globalised 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 already 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 difference between a novel drug and its so-called “me-too” is the speed at which it moves through the regulatory process.

Lastly, 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 that we will examine in much greater detail. Before moving to that discussion however, we should first turn to one last important distinction regarding “me-too’s”.

## “Ever greening” and “me-too” drugs: not the same

In understanding the subtleties of incremental innovation, one must also make clear the distinction between the marketing of new incremental drugs and “ever greening”. Often used synonymously, “ever greening” actually refers to a tactic used by pharmaceutical companies to pre-empt their own patent expirations. Generally, and especially in the case of “block-buster” drugs, generic companies are prepared to enter a particular market immediately after the innovator company’s patent expires. For the innovator company, this typically translates into the loss of 40 per cent of the market to generic manufacturers.<sup>1</sup> In order to diminish the losses experienced when the patent expires, the innovator company may release an improved version of their drug prior to its patent expiration. In doing this, the company has pre-empted the release of generic versions of its “block-buster” drug and perhaps slowed profit losses. While many see this activity 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, incremental innovation represents a much larger and nuanced subject. Therefore, 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 the human species, technological advances tend to occur incrementally, one step at a time. As a result, progress is made over time, as many small steps equal one 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.’”<sup>2</sup> 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.

### Expanding the primary therapeutic unit

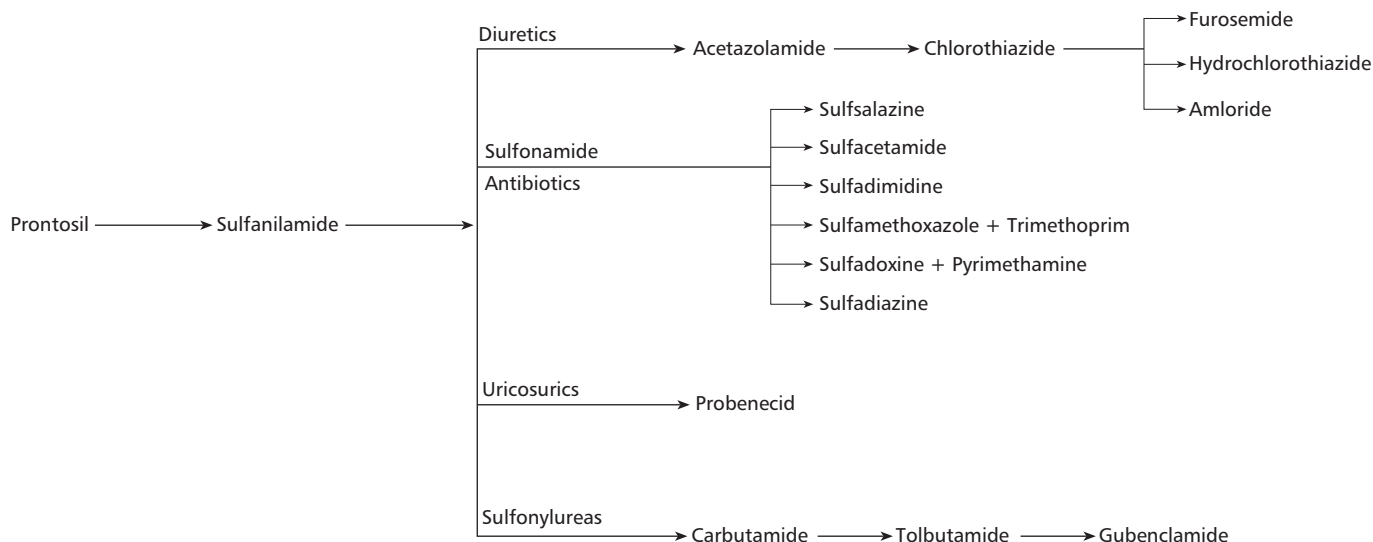
The conglomeration of drugs created through incremental innovation results in the expansion of drug classes. When a breakthrough occurs, a new class is created, thus laying the groundwork for even more innovative advances (see figure 2). As a result of this cycle, and as we would suspect, the pharmacopoeia is characterized by many drug classes, each with its own group of molecularly similar drugs. But within any given class of drugs, each 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 certainly much better to have many options, where 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, each new drug must also represent some cumulative improvement in efficacy, selectivity, and/or reduced toxicity. The end result is a class that is defined by the contributions of its many agents.

### The importance of alternatives

The importance of 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 considering that for some drug classes, particularly those relating to the central nervous system, overall response rates can be as low as 50 per cent to a given class of drugs.<sup>3</sup> For unknown reasons, certain patients respond differently to different drugs within a single class. If physicians have many options at their disposal, they can then calibrate their prescribing patterns to address the needs of specific patients. Drug classes that exhibit high fluidity in overall response rates

Figure 2 **The evolutionary drug innovation process**



include serotonin re-uptake inhibitors (SRIs) and non-steroidal anti-inflammatory agents (NSAIDs).<sup>4</sup>

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 will not lose access to needed medication as a result of regulatory action, warranted or not. There have been innumerable cases where 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 anti-inflammatory agents zomepirac, benoxaprofenm and suprofen, and the fluoroquinolone antibiotic gepafloxacin; 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 ten drugs prescribed in the United States were

products of incremental innovation (Prilosec, Lipitor, Prozac, Prevecid, Zocor, Zoloft, Claritin, Paxil, Norvasc, and Augmentin).<sup>5</sup> Another study, conducted by Wastila et al, examined the World Health Organization's (WHO) Essential Drug List (EDL) and found that half of the drugs represented incremental improvements on older drugs.<sup>6</sup> 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. (See table 1.)

In addition to the more obvious benefits of medicine

Table 1 **Analysis of me-too drugs on WHO's 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).

alternative, there is one other factor that “me-too” opponents fail to grasp. Many developmental projects are begun as blockbuster initiatives, and only later is it realized that the two laboratories are working independently and without the knowledge of the others on a drug development project in the same therapeutic category and even around a similar chemical entity. How rapidly the laboratory work progresses, as well as the phase 1, phase 2, and phase 3 work is not always predictable. Problems such as recruiting volunteers or delays at the CRO make it difficult to determine in advance which is the innovator product when all three files might be delivered to the F.D.A. within a month of each other.

Similarly, 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 USA while product B becomes the first approved in the EU, 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 was not 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 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.<sup>7</sup> 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.<sup>8</sup>

### **Extending the usefulness of breakthrough drugs**

In addition to creating better ways to deliver drug agents, another area of innovation involves the use of new formulations to extend the uses of already existing drugs. In many cases, this process allows a single molecule to be used effectively for several conditions. In other cases, re-formulating leads to new essential drugs such as budesonide inhalation suspension, an inhaled corticosteroid for treating children with asthma. Before this advancement, there were no available inhalers for children with asthma. In this case, the re-formulation of an old drug led to a new and important medicine.<sup>9</sup> 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 stepwise innovation.

#### **Antihistamines**

The original generation of antihistamines provided effective therapy but were characterized by a host of negative side effects including anticholinergic effects, penetration of the blood-brain barrier, and severe drowsiness. Additionally, the therapeutic effect of these drugs dissipated rapidly thus necessitating frequent dosing. The second-generation antihistamines, (i.e. astemizole, loratadine, cetirizine) constituted significant improvements on the originators. These drugs significantly extended the therapeutic effect, reduced penetration of the blood-brain barrier, created no anticholinergic effects, and drastically reduced drowsiness. A new generation of antihistamines (i.e. Allegra), developed from the active metabolites of the second-generation drugs, have led to even greater therapeutic value with increased safety and efficacy profiles.

Table 2 **New fomulations with extended uses**

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

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

## Beta-blockers

The development of beta-blockers into a wide-ranging diverse class of drugs allows physicians to provide individualised 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 (i.e. atenolol, bisoprolol, metaprolol, betaxolol). These new drugs show differences in preserving renal blood flow, dosing schedule, changes in serum lipid levels, sympathomimetic activity, 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 may be seen in table 3, further research and

development work beyond the original propranolol product, resulted in at least eight options for the physician to select from, thus optimising 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, etc. Other less obvious improvements include tablets over capsules, where patients can take a \_ tablet to more precisely customise 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

The development of the 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, patients still react differently to different drugs. Studies analysing the prescription

Table 3 Advantages of selected beta-blockers

	Preserves blood flow to and from the kidneys	Once daily dosing	Reduces mortality after heart attack	No change in blood cholesterol levels	Selectively targets B1 receptors	Equal effectiveness in blacks and whites	ISA <sup>3</sup>	Very low central nervous system penetration	Relaxes blood vessels resulting in improved blood flow
Acebutolol		✓			✓		✓		
Atenolol		✓			✓			✓	
Labetalol	✓			✓		✓			✓
Metoprolol		✓ <sup>1</sup>	✓		✓				
Nadolol	✓	✓						✓	
Pindolol	✓			✓			✓		
Propranolol		✓ <sup>2</sup>	✓						
Timolol			✓					✓	

1 Once a day for hypertension.

2 For controlled-release preparation only.

3 Drug possesses 'intrinsic sympathomimetic activity', which allows blockade of excess stimulation of the 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

patterns of rheumatologists 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.<sup>10, 11, 12</sup>

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.<sup>13</sup> Oral contraceptives have continually been improved to lessen harmful side effects and provide diverse treatment options.<sup>14</sup> Diabetes medications have drastically advanced offering a wide variety of peak effect times allowing physicians to titrate dosing.<sup>15</sup> And antipsychotics have developed to decrease cardiovascular effects.<sup>16</sup> 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 testaments to the importance of supporting innovative endeavours.

## Economic implications

Perhaps the most vehement criticisms thrust upon “me-too” drugs are 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 that the pharmaceutical industry depends on incremental innovations to provide the revenue for 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 eliminated hospital stays.
- Increased worker productivity and less absenteeism.
- Reduced drug costs from increased competition among manufacturers.

### Reduced treatment costs

While the cost of a new drug is a complex compromise between contending parties, which differ from region to region and between countries, it is beyond the scope of

this paper to account for the ultimate cost of drugs. 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 increasing compliance, reducing hospital and physician visits, and increasing worker productivity. Contributions to cardiovascular therapy and the addition of newer 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.<sup>17</sup> 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.

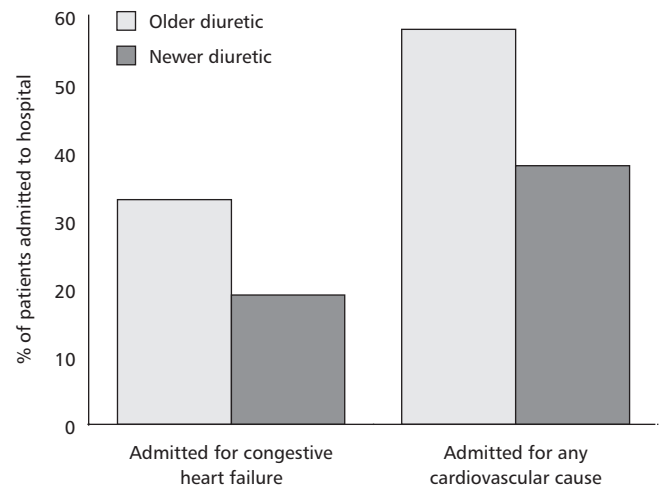
### ACE Inhibitors

A study conducted by Small et al., in 1997, analysed and compared the costs of older versus newer treatment with ACE inhibitors. Utilizing a cohort of 6000 elderly hypertension patients, it was found that the overall median cost per month for treatment with older vs. newer drugs was \$60 and \$53 respectively. It was also found that greater compliance was associated with newer agents when compared to their predecessors, 66 per cent and 58 per cent respectively.<sup>18</sup>

### Reduced hospital costs

In many instances, the introduction of new drugs correlates directly with fewer hospital stays or physicians visits. For example, a study conducted comparing the hospital costs associated with cardiac heart failure (CHF) patients taking the original loop diuretic furosemide compared with those taking the newer torasemide found that the newer drug was associated with reduced costs (see figure 3). Specifically,

Figure 3 **New diuretic associated with fewer hospital admissions**



Source: Stroupe, K.T., Forthefor, M.M., Brater, D.C., & Murray, M.D, "Healthcare costs of patients with heart failure treated with torasemide or furosemide", *Pharmacoeconomics*, 17, 429-440, 2000

those taking the newer torasemide experienced a 16 per cent reduction in CHF related admissions and a 20 per cent 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.<sup>19</sup>

### Increasing productivity

Ultimately, when advances within a class of drugs alleviate debilitating side effects, the result is a quicker recovery period thus resulting in increased work capacity. The example of antihistamines exemplifies the correlation 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.<sup>20</sup> 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 a drastic effect on these figures, leaving workers relatively unaffected by their allergic rhinitis.<sup>21</sup>

Table 4 **New drugs in existing classes tend to be priced at a discount\***

<i>Subclass</i>	<i>Brand name</i>	<i>Launch month and year</i>	<i>Discount relative to weighted mean price (%)</i>	<i>Discount relative to price leader (%)</i>
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	0.0
Macrolides	Dynabae	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
Statins	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 norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

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

Source: DiMasi, J.A. Price Trends for Prescription Pharmaceuticals: 1995–1999. Washington DC: Background report prepared for the U.S. Department of Health and Human Services’ Conference on Pharmaceutical Pricing Practices, Utilization and Costs. 2000.

## Competition

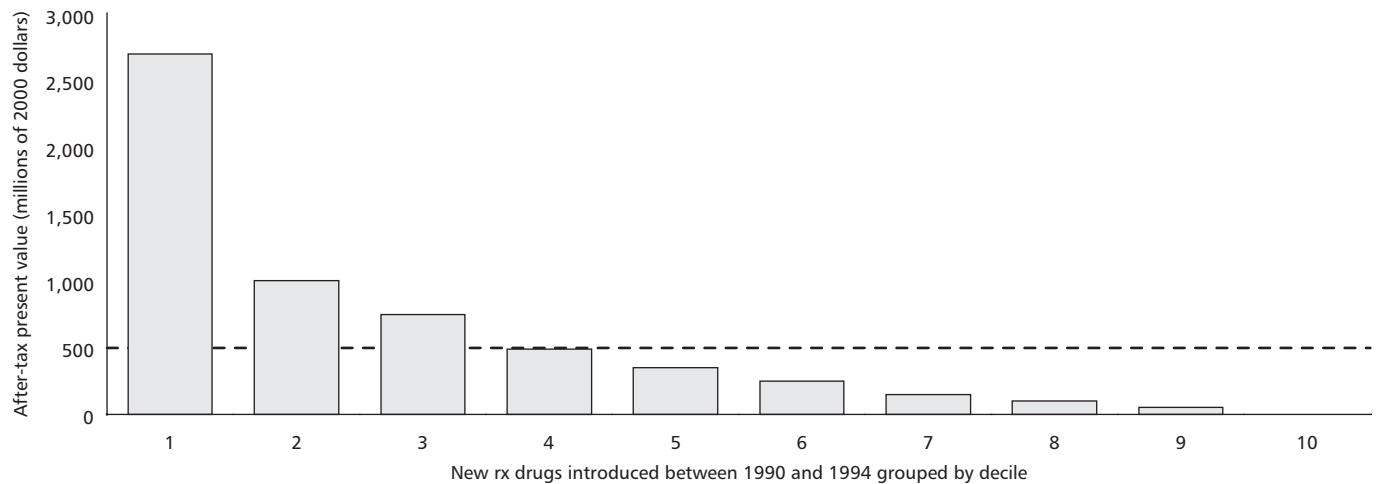
In addition to improving the overall quality of care, incremental innovations also increase competition between drug manufacturers thus lowering drug prices. This effect is not unique to the pharmaceutical industry but is the guiding principle of open markets and free competition. Policies that aim to curb incremental innovation are analogous to advocating the creation of monopolies. In the case of pharmaceuticals, in order for a drug to enter an already established class, it must represent either significant therapeutic improvements or a reduced 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 per cent.<sup>22</sup> 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 the 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. Creating drugs based on incremental innovations provides an acceptable avenue

Figure 4 **Only three out of every ten marketed rx drugs produce revenues that match or exceed average R&D costs**



Note: The drug development costs cited in this chart are out of pocket after tax in 2000 dollars for drugs introduced between 1990 and 1994. The same analysis found that the total cost of developing a new drug was \$802 million.  
 Source: H. Grabowski, J. Vernon and J. DiMasi, 'Returns on Research and Development for 1990s New Drug Introductions', *Pharmacoeconomics* 20, suppl. 3 (2002): 11–29

for pharmaceutical companies to be assured revenue, which can then be used to fuel higher-risk, potential “block-buster” producing 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. 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 as “block-buster” drugs. The reason for this may simply be that “block-buster” 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 “block-buster” 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 any other development-based industry. For the pharmaceutical industry, novel drugs alone are not enough to support the expensive R&D costs. Based 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 advance. 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 be bereft of limitation, but only that limitations should not come in the form of curbing innovation. For sure, other policy actions such as enacting limitations on invasive marketing strategies are needed, and would actually tilt the emphasis scale toward innovation. 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.

## Conclusions

Perhaps extensive pharmaceutical marketing campaigns undercut the reality of real incremental drug innovations. The pharmaceutical industry, like every other industry in today's highly competitive and globalised economy, must find ways to reduce risks while maximising profits – this is no secret. The pharmaceutical industry, however, *is* unique in that it is an extraordinarily and unequalled high risk, high profit industry. Opponents argue that limitations on incremental drug innovations will lead to increased investment, thus 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 endeavours? 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 depending on it.

## Notes

- 1 Schacht, Wendy H.; Thomas, John R. *Patent Law and its Application to the Pharmaceutical Industry: An Examination of the Drug Price Competition and Patent Term Restoration Act of 1984*. CRS Report for Congress: December 18, 2000.
- 2 National Research Council. *Prospectus for National Knowledge Assessment*. National Academy Press, Washington D.C.: 1996.
- 3 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 Health Care Policy and Research, U.S. Department of Health and Human Services, Rockville, 1999.
- 4 Zarate, C.A., Kando J. C., & Tohen, M. et al. Does Intolerance or Lack of Response with Fluoxetine Predict the Same will Happen with Sertraline? *Journal of Clinical Psychiatry*, 57, 67–71, 1996.
- 5 Dorland Healthcare Information. *Market Category A: Pharmaceuticals and Related, All Ethical Pharmaceuticals*. 16th Ed., Vol 1, pp.95–96, Philadelphia, Dorland, 2000.
- 6 Wastila, L.J. Ulcickas, M.E., & Lasagna, L. The World Health Organization's essential drug list. The significance of me-too and follow-on research. *Journal of Clinical Research and Drug Development*, 3, 105–115, 1989.
- 7 Langer R. Drug Delivery and Targeting. *Nature*, 392(679 suppl), 5–10: 1999.
- 8 Starr C. Innovations in Drug Delivery. *Patient Care*, 34(1), 107–137.
- 9 Stapleton, S. Treatment hailed as boon for pediatric asthma patients. *American Medical News*, 43(32), 26, 2000.
- 10 Pincus T., & Callahan, L.F. Clinical use of multiple nonsteroidal anti-inflammatory drug preparations within individual rheumatology private practices. *Journal of Rheumatology*, 16, 1253–1258, 1989.
- 11 Walker A. M., Chan K.W. A., & Wood R.A. Patterns of interchange in the dispensing of nonsteroidal anti-inflammatory drugs. *Journal of Clinical Epidemiology*, 45, 187–195, 1992.
- 12 Jacobs J., & Bloom, B.S. Compliance and Cost in NSAID therapy. *Hospital Therapy*, (suppl), 32–39, 1987.
- 13 Kaplan, N.M. Calcium entry blockers in the treatment of hypertension. Current status and future prospects. *The Journal of the American Medical Association*, 262, 817–824, 1989.
- 14 Miller, J.W. Reproductive Steroids. In: S.G. Carruthers, B.B. Hoffman, K.L. Melmon & D.W. Nierenbergm (eds), *Melmon and Morrelli's Clinical Pharmacology* (4th ed., Ch. 9, pp. 610–636). New York, NY: McGraw-Hill, 2000.
- 15 Miller, J.W. & Kraemer, F.B. Endocrine and Metabolic disorders: Diabetes mellitus. In: S.G. Carruthers, B.B. Hoffman, K.L. Melmon & D.W. Nierenbergm (eds), *Melmon and Morrelli's Clinical Pharmacology* (4th ed., Ch. 9, pp. 529–552). New York, NY: McGraw-Hill, 2000.
- 16 Worrel, J.A., Marken, P.A., Bechman, S.E., & Rueter, V.L. Atypical antipsychotic agents: A critical review. *American Journal of Health-System Pharmacy*, 57, 238–255, 2000.
- 17 Cramer, M.P., & Saks S. R. Translating safety, efficacy and compliance into economic value for controlled release dosage forms. *PharmacoEconomics*, 5(6), 482–504, 1994.
- 18 Small, R.E., Freeman-Arnold, S.B., Goode, J.R., & Pyles, M.A. 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.
- 19 Murray, M.D., Haag, K.M., & Black, P.K., et al. Variable furosemide absorption and poor predictability of response for elderly patients. *Pharmacotherapy*, 17, 98–106, 1997.
- 20 Crystal-Peters, J.C., Crown, W.H., Goetzel, R.Z., & Schutt, D.C. The productivity costs of allergic rhinitis. *American Journal of Managed Care*, 6(3), 373–378, 2000.
- 21 William M Mercer Inc. *Measuring the value of the pharmacy benefit: allergy as a case example*. 17pp, 2000.
- 22 DiMasi, J.A. *Price Trends for Prescription Pharmaceuticals: 1995–1999*. Washington DC: Background report prepared for the U.S. Department of Health and Human Services' Conference on Pharmaceutical Pricing Practices, Utilization and Costs. 2000.

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## Pharmacoevolution: the benefits of incremental innovation

Incremental improvements to medicines are fundamental to enhancing the overall quality of health care. Many of the resulting medicines are inevitably very similar to existing treatments, treating the same ailment(s) in a similar way. Some have claimed that investment in the development of such drugs is wasteful.

However, these drugs often have subtle pharmacological differences which make them more appropriate for specific groups of patients. Some have fewer side effects with certain patients, which confers all manner of advantages, including better compliance and consequently reduced resistance. Others are more efficacious for particular patients. Furthermore, most of the drugs that exist today are the result of a long process of incremental innovation.

From an economic standpoint, increasing the number of medicines within a class results in lower drug prices because it increases competition between manufacturers. Furthermore, pharmaceutical companies depend on incremental innovations to provide the revenue that will support the development of more risky “block-buster” drugs. Policies that aim to curb incremental innovation will ultimately lead to a reduction in the overall quality of medicines in existing classes of drugs, and may ultimately hinder the creation of genuinely novel drugs.

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