TOO MANY DRUGS? THE CLINICAL AND ECONOMIC VALUE OF INCREMENTAL INNOVATIONS

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... it is by no means certain that the increase in productivity over a longer period of time is chiefly due to the great inventors and their inventions. It may well be true that the sum total of all minor improvements, each too small to be called an invention, has contributed to the increase in productivity more than the great inventions have.

Machlup, 1962, 164.

ABSTRACT

Drugs in the same therapeutic class differ in their therapeutic profile, metabolism, adverse effects, dosing schedules, delivery systems, and other features. In addition, such agents can provide backup if the initial drug sometimes fails in the development stage or in the market. The availability of a broad range of medicines enables physicians to treat with precision the individual needs of diverse patients and provides options when the first agent used is either ineffective or not tolerated. Some incremental innovations have been associated with overall cost savings. Competition among drugs in a therapeutic class drives prices down. Policies that limit research on incremental innovations may deny access to important therapies, reduce competition, and erode incentives for research.
I. INTRODUCTION

The process of repeated incremental improvement is the predominant mechanism of innovation and product development within most manufacturing and high-technology industries. The pharmaceutical industry is no exception. This paper explains the value of the incremental pharmaceutical research and development (R&D) process and of having multiple agents in the same pharmacological class.

Incremental advances have generally resulted from molecular modification of existing products, or from independent attempts by drug companies to develop agents with a given pharmacological action. Incremental innovations are often the unintentional result of research aimed towards producing breakthrough products. A company does not know whether it will be first on the market when it initiates a project in a specific therapeutic class.

In addition, companies are also better able to balance their portfolio risk if they combine lower risk, incremental innovation projects with projects geared to produce breakthroughs. Sales of these drugs may help companies to finance their overall research programs (Ketler, 1998).

Some believe that incremental improvements are too costly and do not ultimately benefit the consumer. These criticisms are distilled in a July 11, 2000, quotation from the Financial Times of London:

The debate about pharmaceutical pricing and innovation should focus on how many companies provide real breakthrough benefit for consumers. The answer is: depressingly few. The vast majority of drugs are simply better or worse me-too copies of products that went before them.

Dismissal of new agents in a class as merely “me-too” drugs is predicated on the belief that these agents are essentially identical. This is a misconception. The process of incremental innovation is evolutionary, not duplicative. The new agents resulting from this process can offer advantages in terms of improved efficacy, better patient satisfaction and compliance, and in some cases greater cost-effectiveness. Prescribers need a wide range of choices that include both new and older agents to best treat individual patients.

There are several advantages to having multiple agents within a class, including the following:

• Provision of backup in case an agent is withdrawn from the market;
• Differing dose delivery systems and dosage forms that enable extended uses with a variety of patient populations;
• Availability of choice when patient response to and tolerance of a particular agent is subject to great individual variation;
• The ability to tailor therapy to the needs and preferences of patients; and
• Cost containment due to increased efficacy and, as a result, decreased use of other services (e.g. hospital, office visits).

The development of drug product classes is analogous to the evolution of biological species, and the advantages of diversity within groups of pharmaceutical products are similar to the advantages of biodiversity. "Pharmacodiversity" ensures the stability and viability of the drug group. Competition exists for survival in a changing environment, and lack of diversity could doom a species or lineage to extinction. Within a drug class, products with varying features compete for patients. Over time, the emergence of new disease and patient targets expands the role of some agents; but others are disadvantaged by newly discovered adverse effects. Thus, those products that are best "fit" for their environment dominate the marketplace; others may become extinct; and still others maintain positions in “niche markets.”

In this paper we explain the benefits of developing a therapeutic class comprised of multiple agents with somewhat different properties; document the valuable, often unanticipated uses of these agents in numerous diseases; and show that incremental innovations can be cost-effective.

II. THE EVOLUTION OF PHARMACEUTICAL THERAPIES

Most technological advances are built from bits and pieces rather than from large leaps or breakthroughs in discovery or technology. This means that the products of technology-driven industries improve as a result of a series of small steps forward. Over time, a succession of small wins adds up to a big advance in technology. The importance of small wins in the success of most enterprises is often underestimated. "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' " (National Research Council, 1996).

The value of incremental innovation in medical technology is illustrated by the case of computerized tomography (CT) scanning technology. A detailed econometric analysis of the diffusion and use of a succession of improved CT scanners in U.S. medical facilities estimated a social rate of return of about 270% (Trajtenberg, 1990). The gains accruing to consumers from successive innovations in scanning technology greatly exceed the amount they paid for these services.

Great strides in pharmacology and therapeutics have resulted from very small variations in the chemistry of active molecules (Maxwell, 1984; Maxwell &
Eckhardt, 1990). In fact, the history of pharmacology is characterized by incremental improvements in the safety, efficacy, selectivity, and utility of drugs within a given class. As a result, many pharmacological classes now contain numerous agents. Although these agents are molecularly similar, their therapeutic properties are often significantly different. The public benefits are striking because a broad class of drugs enables physicians to treat with precision the individual needs of diverse patients.

**The Drug Class as the Fundamental Therapeutic Unit**

Although “breakthrough” therapies attract public attention, small, successive developments make a great difference for many patients. Breakthrough products, which are usually the first of a class, inevitably display deficiencies after they are widely distributed. Pharmaceutical companies use these revealed deficiencies as opportunities to develop related compounds that are more effective, more selective, and less toxic.

A novel therapeutic entity is best seen as the organizing principle for the eventual evolution of a new class of agents. In time, other drugs with similar properties are discovered and developed. The drug class as a whole eventually becomes the fundamental therapeutic unit. The therapeutic power, stability, and utility of a class are defined through the contributions of its multiple agents. Features that emerge only at the class level include:

- Variability in pharmacological properties to fit the needs of individual patients;
- Cumulative improvements in efficacy, selectivity, and reduced toxicity;
- Comprehensive knowledge of the extent and limits of pharmacological action, derived from research and clinical experience with multiple chemically related agents; and
- Availability of a “tool chest” for further research on basic disease mechanisms.

Because of these attributes, the collective therapeutic advantage of the class as a whole may be of greater clinical significance than the original advantage of the pioneer compound.

**The Collective Advantage: Alternative Agents for Treatment Failure**

One of the most important reasons for having multiple drugs within the same pharmacologic class is that many drugs, particularly those for diseases of the
central nervous system, have overall response rates of 50% or less (cf. Williams et al., 1999). For reasons that often are not clear, patients who fail to respond to one drug will respond to another agent of that class. Examples of widely used drug classes associated with great individual variation in patient response are the selective serotonin re-uptake inhibitors (SSRIs) and the non-steroidal anti-inflammatory agents (NSAIDs). In patients treated with SSRI agents for depression, 26% of non-responders to fluoxetine did respond to sertraline (Zarate et al., 1996). Conversely, another study reported that 63% of patients who failed to respond to sertraline did respond to fluoxetine (Thase et al., 1997). In a third report of switching from one SSRI to another, the overall success rate averaged 51% (Joffe et al., 1996). The NSAIDs also differ greatly with respect to efficacy and patient tolerance; often, multiple agents must be tried before success is achieved (see Non-steroidal anti-inflammatory agents, below).

The Collective Advantage: Provision of Back-up

The availability of multiple agents in a class provides a backup in the event that a drug is eventually found to have unacceptable side effects. A recent example is the case of the thiazolidinediones, a new class of oral antidiabetic agents that improve hyperglycemia by increasing insulin sensitivity. The first agent of this class, troglitazone, was approved in 1997 but was withdrawn from clinical use in the United States in April 2000 due to hepatotoxicity. Fortunately, two second-generation thiazolidinediones – rosiglitazone and pioglitazone – were introduced in mid-1999 and appear to have less hepatotoxicity. Other examples include the anti-inflammatory agents zomepirac, benoxaprofen, and suprofen; the antihistamines terfenadine and astemizole; and the fluoroquinolone antibiotic grepafloxacin. Wide clinical experience revealed infrequent but important side effects of these agents, requiring them to be withdrawn from the market.

The need for backup drugs is well illustrated by the case of Bendectin, the only drug effective in treating severe morning sickness during pregnancy. Severe nausea and vomiting can lead to serious maternal nutritional deficiencies and nerve damage, as well as a possible increase in birth defects. Merrell Dow reluctantly withdrew Bendectin in 1983 because the cost of lawsuits alleging damage from birth defects exceeded revenues from the product. Since there are still no backup products, withdrawal of Bendectin has left a significant therapeutic gap. This situation is especially tragic since the great preponderance of evidence exonerates the drug from any harmful effects (Skolnick, 1990).
Breakthrough therapies inevitably display deficiencies after they are widely distributed, and they are eventually replaced in the marketplace by improved agents. Most of the top 10 prescription drugs sold in the United States in 1999 (Prilosec, Lipitor, Prozac, Prevacid, Zocor, Zoloft, Claritin, Paxil, Norvasc, and Augmentin) (Dorland, 2000) represent incremental improvements.

New agents in a drug class often become “essential therapy.” A study by the Center for the Study of Drug Development at Tufts University analyzed the composition of the World Health Organization’s Essential Drug List. This list has been globally accepted as a standard of basic therapy for developing countries where more sophisticated medicine is not feasible. Almost half of the drugs were found to be replacement compounds (Wastila et al., 1989). The presence of these replacement drugs on the WHO Essential Drug List is further evidence that “research dedicated to improving efficacy and safety profiles of innovator drugs, as well as discovering new therapeutic uses, is of medical importance to both developed and underdeveloped nations” (Wastila et al., 1989).

The early history of the beta-blockers illustrates a dynamic pattern of drug replacement. Figure 1 traces the market share of the five most successful beta-blockers available between 1970 and 1986 (Wells, 1988).

The launch of product C in 1970 appeared to herald the arrival of a new chemical entity of major significance. Within 2 years it had become the market leader, capturing 43% of the market share. But in 1974, this beta-blocker was found to have serious side effects that led rapidly to its withdrawal from the market entirely.

Seven different beta-blockers were on the market when product D was introduced in 1976. In contrast to product C, product D had gained only 13% of the market share within 2 years. However, subsequent use of product D in clinical practice showed that it possessed advantages over competitors’ products, and in 1986 it was the most heavily prescribed beta-blocker in the primary care setting, capturing a market share of 49%.

The first drug in this series (product A) rapidly achieved a level of acceptance that fluctuated over time. The market share of product B increased steadily for a few years after launch, only to be followed by an equally steady decline in use. And product E appeared to be useful for only a small number of patients and never achieved a substantial market share.

Figure 1 shows the considerable variation in the patterns of acceptance achieved by individual beta-blockers. The perceived clinical value at the time of introduction does not predict a product’s eventual success.
III. ADVANTAGES OF ADVANCED DOSE DELIVERY SYSTEMS AND DOSAGE FORMS

Dose Delivery Systems

The main drawback of traditional dosage forms is lack of control over how the drug is released or absorbed. Fast absorption, for example, may cause adverse effects or require frequent dosing. Advanced delivery systems provide sustained therapeutic drug levels for ever-longer periods of time (Langer, 1999). These systems also can enable the use of smaller or fewer doses, a less invasive mode of administration, and prolonged circulation of short-lived compounds. Examples of advanced delivery systems are given below.

Transdermal delivery. With transdermal delivery, a polymer membrane controls the rate of drug delivery into the systemic circulation, resulting in far better control than that achievable with depot injections of water-soluble formulations. Transdermal delivery of the synthetic opiate fentanyl provides continuous analgesia for 3 days, and transdermal estrogen replacement patches release estradiol for up to a week. Transdermal patches are particularly useful for postmenopausal women who either become nauseated when they take oral estrogens or have

![Graph showing market share of beta-blockers from 1970 to 1986.](image-url)
elevated triglyceride levels, since the latter are less likely to be increased with transdermal administration (Starr, 2000).

Other agents incorporated into transdermal delivery systems are clonidine, nicotine, nitroglycerin, lidocaine, and testosterone. For example, the local anesthetic lidocaine has recently been formulated in a patch for treatment of postherpetic neuralgia, a painful complication of shingles. By delivering a constant, low level of drug to the skin, the patch relieves pain without the sensory block that results in numbness.

Delayed-onset, extended-release oral formulations. Such formulations of the calcium channel antagonist verapamil represent the first chronotherapies for hypertension (Smolensky, 1999). These formulations are taken before bedtime, and drug release is delayed for 4 to 5 hours so that peak blood levels occur almost 11 hours after ingestion and are highest when patients awaken. This pattern of release parallels the circadian increase in blood pressure and increased incidence of angina, heart attacks, and stroke early in the day.

Sustained-release formulations enable less-frequent dosing, the importance of which should not be underestimated. For example, taking Concerta, a new 12-hour formulation of methylphenidate (Ritalin), in the morning eliminates the need for children with attention deficit disorder to take a dose during or after school hours. This obviates the need for storage and supervision of the medication during school hours.

Liposomes. When the antifungal agent amphotericin B is encapsulated within small lipid vesicles (liposomes), the drug remains in the bloodstream longer and concentrates in areas of increased capillary permeability, such as sites of infection (Hebel, 1998). Toxicity is diminished by reducing exposure to normal tissues. Other very potent compounds now delivered in liposome delivery systems are daunorubicin and doxorubicin, both used to treat AIDS-related Kaposi’s sarcoma (Starr, 2000).

Polymers. Polymers have been used in a variety of delivery systems that allow drugs to be delivered at constant rates over days, months, or even years. A polymer matrix is used to deliver the cancer drug carmustine directly to the brain after surgery for recurrent glioblastoma. Wafers impregnated with this potent drug are placed in the remaining cavity after removal of the accessible tumor. Theagent diffuses into the brain tissue over the course of about 1 month, killing the remaining malignant cells while minimizing systemic adverse reactions. The polymer does not need to be removed since it eventually degrades (Starr, 2000).
Reformulation can result in important new applications for the reformulated drugs. Table 1 illustrates how reformulation has extended the uses of some medications.

A recent example of a new formulation that has greatly extended the use of a medication is budesonide inhalation suspension (Pulmicort Respules), an inhaled corticosteroid preparation for treating asthma in children under 4 years of age (Stapleton, 2000). Corticosteroids are used for maintenance therapy to reduce airway inflammation that precipitates severe asthma attacks. The new formulation relies on a jet nebulizer that uses pressurized air to disperse the medication in a fine mist; the child inhales the mist through a face mask or
mouthpiece. Previously, there were no inhalers in the United States that small children could use properly. The ability to control asthma early on in very young children and prevent “airway remodeling” is expected to have long-term benefits (Stapleton, 2000).

**Single Isomer Forms**

Some drugs are now being remanufactured in their purer single-isomer forms. These agents can have the full therapeutic effect of the original (racemic) medication without unwanted effects associated only with the discarded isomer. For example, the recently introduced agent levalbuterol contains only the isomer exclusively responsible for the bronchodilating effect of albuterol, a beta-agonist agent used to treat asthma. The discarded isomer has no therapeutic effect, interferes with the overall efficacy of the drug, and may cause detrimental airway hyperactivity. Levalbuterol appears to be more potent than albuterol and requires a lower dose to achieve bronchodilator effects. Consequently, fewer beta-agonist side effects are experienced, which is especially important for children and elderly patients with cardiovascular, thyroid, and other conditions that are aggravated by beta-agonist actions (Portyansky, 1999).

**IV. MATCHING PATIENTS’ NEEDS: MULTIPLE AGENTS FOR PHARMACOLOGICAL VARIABILITY AND CHOICE IN MAJOR THERAPEUTIC CLASSES**

Many of the major classes of drugs in current use owe their overall therapeutic effectiveness and clinical significance to important modifications in the first generation of drugs. Introducing new compounds within a class leads to either a whole new generation of agents or to a diversity of effects. These concepts are illustrated by the incremental innovation within 11 major drug classes: antihistamines, beta-blockers, calcium channel blockers, cephalosporin antibiotics, NSAIDs, oral contraceptives, sulfonylurea hypoglycemic agents, insulin preparations, atypical antipsychotics, anesthetics, and endocrine therapy for breast cancer.

**Antihistamines**

First-generation antihistamines, which are based on the structure of histamine, are short-lived, require multiple dosing, and penetrate the blood-brain barrier, producing sedation and interfering with histamine use in the brain. These agents also have anticholinergic effects such as dry mouth. Second-generation
antihistamines (astemizole [Hismanal], loratadine [Claritin], cetirizine [Zyrtec]) are more specific blockers of H₁ receptors and penetrate the brain to a lesser extent. These improvements are associated with longer therapeutic activity, less frequent dosing, no anticholinergic side effects, and limited sedation.

The first-generation antihistamines produce driving impairment similar to that produced by alcohol, while second-generation agents produce minimal impairment at standard doses. The policies of the Federal Aviation Administration reflect the relative safety of the second-generation antihistamines; pilots are allowed to fly while taking second-generation, but not first-generation, drugs (Seidman, 2000).

Third-generation antihistamines are now being developed from the active metabolites of the second-generation agents. These drugs retain the activity of the parent compound but with improved tolerability, improved pharmacokinetics, fewer side effects, and greater safety.

For example, terfenadine (Seldane) has been replaced by its fast-acting metabolite fexofenadine (Allegra). Fexofenadine and terfenadine both act by binding to the same receptor and exhibit the same clinical efficacy. But terfenadine was found in some rare cases to build up and bind to a potassium receptor in the heart, causing cardiac arrhythmias (especially in the presence of certain antibiotics), liver dysfunction, or cardiovascular disease, and was withdrawn from the market. Astemizole also was withdrawn for similar reasons. The enhanced safety profiles of the third-generation agents (i.e., fewer cardiac arrhythmias and drug-drug interactions) are being realized.

**Beta-Blockers**

The many beta-blockers produced by pharmaceutical companies after the introduction of propranolol illustrate the advantages of a fully developed class of drugs.

The currently available beta-blockers offer differences in potency, cardioselectivity, effects on the nervous system, pharmacokinetic properties (which determine appropriateness for patients with impaired kidney or liver functioning), additional pharmacological effects, potential for interaction with other drugs, efficacy in specific racial groups, complexity of the dosage regimen, and adverse effects profile. This array of differences enables doctors to customize treatment to the patient’s specific needs. Another advantage is that undesirable side effects in an individual patient can be avoided by switching to another member of the class.

Several generations of beta-blockers have appeared over the last few decades. Compared with first-generation beta-blockers, second-generation agents, which are selective for beta₁ receptors (e.g. metoprolol, atenolol, bisoprolol, ...
**Table 2.** Selected Advantages of Individual Beta-Blockers (Frishman, 1987).

<table>
<thead>
<tr>
<th>Advantage</th>
<th>Acebutolol</th>
<th>Atenolol</th>
<th>Labetalol</th>
<th>Metoprolol</th>
<th>Nadolol</th>
<th>Pindolol</th>
<th>Propranolol</th>
<th>Timolol</th>
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<tr>
<td>Preserves renal blood flow</td>
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<tr>
<td>Once-a-day dosing</td>
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<td>X</td>
<td>X°</td>
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<tr>
<td>Reduces mortality after heart attacks</td>
<td>X</td>
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<td>No change in serum lipid levels</td>
<td>X</td>
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<td>X°</td>
<td>X</td>
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<tr>
<td>β₁ selectivity</td>
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<td>X°</td>
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<td>Equal effectiveness in blacks and whites</td>
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<td>Intrinsic sympathomimetic activity</td>
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<td>X</td>
<td>X°</td>
<td>X</td>
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<td>Very low central nervous system penetration</td>
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<td>X</td>
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<td>Vasodilation</td>
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a Once a day for hypertension.
b For controlled-release preparation only.
betaxolol), are not as likely to produce systemic vasoconstriction. Thus, they may benefit patients with mild to moderate heart failure when used in combination with angiotensin-converting enzyme (ACE) inhibitors. Third-generation beta-blockers (e.g. carvedilol, labetalol, pindolol, sotalol) may have even better myocardial protective properties.

Each of the currently marketed beta-blockers has its own unique profile of attributes and drawbacks that derives from its pharmacological properties. Table 2 compares the special properties and clinical indications of some of these agents. Since individual patients will differ in their requirements for each feature, no single agent is optimal for every patient.

**Calcium Channel Blockers**

Agents that block the influx of calcium into muscle cells have rapidly gained importance in the treatment of hypertension, angina, cardiac dysrhythmias, heart failure, cardiomyopathy, stroke, and other cardiovascular conditions. They act on vascular smooth muscle to cause dilation and suppression of vasospasms and on the myocardium to decrease contractility, conductance, and automaticity. However, since the relative strength of these effects varies among the agents of the class, specific agents can be differentially effective in a given condition. For example, they are similar in their effectiveness against hypertension and angina but differ in the extent of their actions on the circulatory system.

The first agent to become available was verapamil, a derivative of the cerebral vasodilator papaverine. Compared with subsequently developed agents in this class, verapamil can have marked effects on cardiac contractility and rate and also can slow the conduction of electrical impulses within the heart. As a result, verapamil is useful in treating irregular heart rhythms.

Compared with verapamil, nifedipine (the prototype agent of the dihydropyridine subclass of calcium channel antagonists) is a relatively selective dilator of peripheral smooth muscle. Diltiazem lies somewhere between verapamil and nifedipine in its balance of effects on heart versus peripheral vasculature (Hoffman & Carruthers, 2000). Physicians exploit these differences in selectivity in choosing the most appropriate agent for an individual patient.

More than a dozen calcium channel antagonists with a wide range of chemical structures are now available in the United States. Agents in the largest group, the dihydropyridines, have different sites and modes of action on calcium entry into smooth and cardiac muscle cells. Second-generation dihydropyridines have more selective actions than first-generation agents. For example, nicardipine targets vascular muscle rather than cardiac muscle, which means more dilation of heart and peripheral blood vessels but less depression of the
heart’s ability to contract. This difference may be of particular advantage to hypertensive patients who also have congestive heart failure (CHF) (Enigbokan, 1989). Second-generation agents with no depressant effect on the heart may also provide cardioprotection not demonstrable with the first-generation drugs (Kaplan, 1989). Some second-generation dihydropyridines, (e.g. amlodipine) have a slower onset of action and a longer half-life, allowing for once-daily dosing (Michel & Weinfeld, 2000).

Various dihydropyridines also may differ in their ability to cross the blood-brain barrier and in their effectiveness in dilating blood vessels of the brain. Nimodipine and nicardipine have been shown to enter the brain, dilate cerebral blood vessels, and protect against brain ischemia. Nimodipine improves survival and neurological outcome after acute ischemic stroke and is also useful in treating complications of subarachnoid (brain) hemorrhage (Kaplan, 1989).

Cephalosporin Antibiotics

The inevitable emergence of antibiotic-resistant bacterial strains has been the driving force in the development of new antibiotics. Structural modifications have produced multi-generation families of penicillins, quinolones, aminoglycosides, cephalosporins, and others that have provided therapies for resistant bacteria. In addition, successive generations within a family are often effective against more types of bacteria; in other words, they have a broader spectrum of activity.

Almost all of the currently marketed cephalosporins represent chemical modifications of the basic cephalosporin structure. Sharing a common ring structure, cephalosporins are characterized as first-, second-, third-, or fourth-generation agents.

First-generation cephalosporins offer therapy primarily for gram-positive bacterial infections, while second-generation agents provide broad-spectrum gram-negative coverage. Some second-generation agents provide anaerobic coverage. Although most of these agents are effective only in injectable form, several first- and second-generation cephalosporins have the advantage of being effective when given by mouth.

Third-generation agents provide broad-spectrum gram-negative coverage. Compared with second-generation agents, third-generation cephalosporins exhibit a marked increase in potency against gram-negative bacteria and increased resistance against beta-lactamase destruction. Some third-generation agents also have substantial antipseudomonas activity. Generally, third-generation cephalosporins are less active than first- and second-generation agents against gram-positive bacteria and anaerobes. Less frequent dosing is also
possible with some third-generation agents. These agents penetrate inflamed meninges (membranes covering the brain and spinal cord), extending the therapeutic uses of cephalosporins.

Fourth-generation agents have broad-spectrum gram-negative activity (including anti-pseudomonas activity) and gram-positive activity comparable to that of first-generation agents.

The wide range of therapeutic choices provided by the class of cephalosporin antibiotic agents gives the physician:

• The ability to tailor treatment to combat gram-positive infection, mixed infections, or anaerobic infections;
• The availability of injectable, topical, and oral dosage forms; and
• Choice between short-acting and long-acting agents, depending on the nature of the bacterial infection, including bacterial strains heretofore resistant to existing antibiotics.

Non-Steroidal Anti-Inflammatory Drugs

Non-steroidal anti-inflammatory drugs are widely used in the treatment of various forms of arthritis and other inflammatory diseases. It is difficult to predict a patient’s response to a particular agent, and tolerance and clinical response to a given NSAID vary widely among patients. Since no clear-cut guidelines exist to help predict the therapeutic success of any NSAID for an individual patient, multiple agents must be available to meet the specific needs of individual patients.

Studies of physician prescribing patterns indicate that doctors utilize the full range of available agents. Rheumatologists were found to use 8 to 12 NSAIDs in treating rheumatoid arthritis patients, and no single agent was used by more than 15% of patients (Pincus & Callahan, 1989). And regardless of which NSAID is used first, it is often necessary to try a second or third agent before finding one that produces the desired response.

Abenhaim et al. (1991) found a 27% switching rate among NSAIDs over the course of 1 year. Walker et al. (1992) found that switching occurred with 8% of prescriptions, due primarily to inefficacy as opposed to adverse reactions. During one 2-year study, 49% of patients were switched to another NSAID; 20% were switched two times or more; and 7% received four or more different NSAIDs (Jacobs & Bloom, 1987).

Although the NSAIDs differ in their effects on individual patients, these agents all have similar effectiveness and side effect profiles. It seemed that further diversity would be unlikely to add value to this mature class. However, in 1999 the vitality of the NSAID class re-emerged with the introduction of
the first cyclooxygenase-2 (COX-2) inhibitors (celecoxib [Celebrex] and rofecoxib [Vioxx]), which offer side effect advantages (mainly related to gastrointestinal effects) over previous NSAID products. As a result of these incremental advantages, these new agents are forecast to be among the top 10 products prescribed worldwide within only a few years (Wood Mackenzie Consultants, 2000).

Oral Contraceptives

The first estrogen-progestin combination oral contraceptive (OC) was approved by the Food and Drug Administration (FDA) in 1960. Formulations of OCs were changed in response to epidemiological studies linking the risk of serious cardiovascular side effects with the steroid content of OCs. Sequential OCs – introduced in 1965 – were subsequently withdrawn from the U.S. market, largely because of epidemiological findings related to endometrial cancer.

As a result, OCs have evolved from high-strength and high-potency drugs to much lower strength, lower potency drugs. Low-estrogen OCs were first marketed in 1967; by 1976 they dominated the market, accounting for 85% of the OCs dispensed in 1984 (Piper & Kennedy, 1987). The multiphasic OCs represent another incremental advance. The amount of drug in each pill within a cycle has been carefully adjusted, further lowering the total dose administered over the use cycle.

Advances in the delivery of contraceptives provide a long-acting effect and simplify dosing. Intramuscular implants of progestin-only contraceptives provide effective contraception for 5 years with an annual pregnancy rate of less than 1% (Sivin, 1988). This very effective, reversible new method of contraception represents an important alternative that overcomes the substantial compliance problems associated with traditional OCs.

Newer synthetic progestins (i.e. desogestrel, norgestimate, gestodene) allow significant reductions in estrogen dosage in combined contraceptive agents and have relatively fewer androgenic effects (Miller, 2000). Combined with ethynyl estradiol, these progestins represent improved oral contraception, offering not only efficacy and safety, but also fewer side effects, including low rates of breakthrough bleeding, cycle irregularity, amenorrhea, nausea, weight gain, acne, and excess hair growth.

The many choices among available combined OCs allow for individualized care. Breakthrough bleeding may improve with a product that has a higher progestin content. Nausea and weight gain may be minimized by a preparation with a lower dose of progestin. Patients with hirsutism or acne may benefit from a higher estrogen dose or a new generation progestational preparation
These choices help meet the diverse and changing needs and preferences of women throughout their reproductive lives.

**Diabetes Medications**

Increasing recognition that tight glycemic control significantly reduces the vascular complications of diabetes (Diabetes Control and Complications Trial Research Group (1993, 1998, 2000) has led to more aggressive treatment of patients with type 1 and type 2 diabetes. New oral agents and insulin analogs developed in the mid-1990s have contributed substantially to our ability to improve glycemic control by targeting insulin resistance and insulin secretory defects as well as by targeting both fasting and postprandial blood glucose levels with minimal risk for hypoglycemia. These new agents now provide more options for achieving tight glycemic control and allow individualized treatment.

**The Insulin Family**

The insulin molecule has been manipulated extensively to produce a range of insulin products that vary in their time of onset and duration of action. Intensive treatment regimens often utilize several types of insulin, injected at different times of the day. Onset times range from 15 minutes to 4 hours; peak effect times range from 1 to 24 hours (Miller & Kraemer, 2000). Premixed preparations of insulins with different onset and duration times offer added convenience, improved compliance, greater dosage accuracy, and reduced risk of hypoglycemia. These mixtures are especially useful for physically impaired patients who have difficulty preparing an insulin injection from two vials.

The development of this array of insulin products began with the advent of longer-acting agents, made by adding zinc and protamine to form crystalline insulin suspensions. Human insulin, prepared by chemical modification of porcine insulin and by recombinant DNA technology, became commercially available by 1980. The use of human insulin has made immunological responses to impurities rare. In the 1990s, modification of key amino acids in soluble, noncrystallized insulin led to the production of rapidly acting, short-duration insulin analogs.

In addition to innovations in insulin synthesis, technical improvements in insulin delivery have led to continuous subcutaneous insulin infusion and convenient pen-type multiple-dose injection devices. Pulmonary, nasal, and oral administration methods are in various stages of clinical development.

The upcoming insulin nasal sprays will be a boon for a variety of reasons. They will be a plus for individuals who are squeamish about injections, and...
they will reduce infections and injection site problems, including accidental needle sticks. They will negate the need for needles and syringes, which add acquisition costs as well as large disposal costs and concerns. Diversion of syringes and needles to drug abusers and the potential for transmission of human immunodeficiency virus (HIV) via needles will be eliminated.

**Sulfonylurea Agents**

Starting with the original agent tolbutamide (itself derived from antibacterial agents), six drugs of similar molecular structure are currently available for the treatment of non-insulin-dependent diabetes. They differ widely in potency, duration of action, dose range, metabolism, side effects, convenience, and potential for interaction with other drugs. This variety of characteristics enables the matching of an agent to the patient’s nutritional status and dietary habits, age, concomitant medications, and other medical conditions (Gerich, 1989; Melander et al., 1989). Examples include the following:

- Potent, long-acting sulfonylurea agents should not be prescribed for elderly patients with poor dietary habits.
- Patients with severe renal insufficiency should not be treated with those sulfonylurea agents that may accumulate.
- Several sulfonylurea agents are often effective in single daily doses and, for some patients, may be associated with better medication compliance than agents that must be taken more frequently.
- Some sulfonylurea agents are manufactured in a wide dose range, enabling more precise dosing.

The second-generation sulfonylurea hypoglycemic agents are more potent than the first-generation agents and thus can be used in smaller quantities per day. Also, troublesome side effects occur less frequently with these newer agents, and there appears to be reduced potential for interaction with other frequently used drugs (e.g. aspirin).

**More Innovation Required**

Although many choices and combinations of therapy are available, most patients with diabetes still do not achieve sustained normal blood sugar levels and are prone to hypoglycemia and other metabolic abnormalities, with consequent vascular complications. Multiple daily boluses of insulin, however finely tuned, do not mimic normal insulin physiology; and current oral therapies are not suited for some groups of patients. Thus, despite the large number of available medications, more agents in these drug classes are needed. For example, since the liver is relatively under-insulinized with current insulin preparations,
synthetic insulin analogs with a greater affinity for the liver may provide better metabolic control. Such agents are in development (Shojaee-Moradie et al., 2000).

**Atypical Antipsychotics**

The atypical antipsychotics are revolutionizing the treatment of psychosis and schizophrenia. Unlike the neuroleptics (haloperidol), they improve negative symptoms (withdrawal, poverty of speech and movement) as well as positive symptoms (hallucinations, conceptual disorientation), are effective in treatment-resistant schizophrenia, and cause minimal motor reactions.

The first of these agents, clozapine (Clozaril), was introduced in the United States in 1990. Although clozapine does not cause motor reactions, it has other significant side effects, including sedation, hypotension, salivation, and most importantly agranulocytosis – a rare but potentially fatal blood disorder requiring strict monitoring.

These drawbacks inspired the search for other agents. Risperidone (Risperdal, introduced in 1995) does not cause agranulocytosis; is effective in patients with refractory schizophrenia, including negative symptoms; and causes minimal motor or cardiovascular effects at therapeutic dosages. Olanzapine (Zyprexa, introduced in 1996) and quetiapine (Seroquel, introduced in 1998) have chemical structures similar to that of clozapine, do not cause agranulocytosis, and also have minimal motor effects.

**Table 3. Adverse-Effect Profiles of Atypical Antipsychotics**

(adopted from Worrel et al., 2000).

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Severity&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Clozapine</th>
<th>Risperidone</th>
<th>Olanzapine</th>
<th>Quetiapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergic effects</td>
<td>+++</td>
<td>0</td>
<td>++</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Agitation</td>
<td>0</td>
<td>++</td>
<td>+&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0/+</td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>+++&lt;sup&gt;b&lt;/sup&gt;</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Sedation</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Orthostatic dizziness or hypotension</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Prolactin elevations</td>
<td>0</td>
<td>+&lt;sup&gt;b&lt;/sup&gt;</td>
<td>+++&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Weight gain or increased appetite</td>
<td>+++</td>
<td>++</td>
<td>+++&lt;sup&gt;b&lt;/sup&gt;</td>
<td>+&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> 0 = none, 0/+ = minimal, + = mild, ++ = moderate, +++ = severe.

<sup>b</sup> Dose-related effect.
All of these agents, and others in development, have a place in the treatment of schizophrenia. Their adverse effect profiles differ (Table 3), enabling individualized treatment. For example, selection of a drug with limited anticholinergic adverse effects is advised for patients in whom cholinergic function is already impaired (Worrel et al., 2000).

The atypical antipsychotic agents improve the capacity of schizophrenic patients to function in work and social settings. By improving cognitive and vocational ability, these agents have mitigated the lost productivity responsible for the estimated billions of dollars in annual indirect costs of schizophrenia in the United States (Rupp & Keith, 1993; Wyatt et al., 1995).

Although the atypical agents all improve cognition, they appear to differ in their effects on several domains of cognitive function (Keefe et al., 1999; Meltzer & McGurk, 1999). Clozapine favorably affects motor skills and verbal fluency; olanzapine improves verbal learning and verbal memory, but in preliminary studies it did not improve visual learning and visual memory; and risperidone improves attention and executive functions, but not verbal fluency and motor learning, with no data available on its effect on visual learning and visual memory (Keefe et al., 1999; Meltzer & McGurk, 1999).

Meltzer and McGurk (1999) foresee characterizing patients with schizophrenia based on their deficits in specific domains of cognition and selecting drugs based on selective properties likely to correct those deficits. They suggest that “risperidone may be prescribed for patients with particular deficits in working memory and executive function, and clozapine or olanzapine for patients with deficits in verbal fluency.”

Anesthetics

The continuing trend toward outpatient surgery is in large part possible due to the introduction of improved anesthetic agents with more rapid onset, shorter duration of effect, and fewer untoward side effects (e.g. respiratory and cardiac depression). Outpatient surgery is generally preferred by patients, avoids the costs and risks of hospitalization, and is associated with less postoperative pain and fewer side effects. Advances in anesthetic agents have also made many new surgical techniques possible.

Thanks to these advances, mortality directly attributable to anesthesia is now rare. In addition, recent innovations have contributed to an important decrease in morbidity from anesthesia and to improved perioperative management. Some important pharmaceutical innovations in anesthesia are summarized below (Fox, 1999).
New inhalation agents allow rapid, pleasant induction of anesthesia and rapid recovery with minimal “hangover.” Desflurane, recently introduced for maintenance anesthesia, allows precise control of anesthesia depth and very rapid recovery. The newly introduced agent sevoflurane is highly insoluble in blood and therefore has the advantages of rapid induction and recovery and easy control of anesthesia depth. Induction with sevoflurane is smooth because it does not irritate the airways.

Remifentanil is a new, potent synthetic opioid ideally suited for intravenous infusion during anesthesia. Its half-life is less than 10 minutes. Furthermore, the half-life is not affected by duration of infusion (which makes it unique among the opioids). Remifentanil is now widely used during neurosurgery and is likely to represent a significant advance in several other areas (e.g. cardiac and cardiovascular surgery).

Chemical separation of stereoisomers has allowed the development of safer local anesthetics. The S (-) isomer of bupivacaine is as effective as unseparated bupivacaine but probably represents a significant advance in safety since it causes less cardiovascular disturbance. The S (-) isomer of the new local anesthetic ropivacaine, a close relative of bupivacaine, produces equivalent anesthesia but has a superior central nervous system and cardiovascular toxicity profile. Epidural administration of ropivacaine has been reported to allow good analgesia with less intense motor block than bupivacaine.

Postoperative nausea and vomiting remain significant problems after general anesthesia. The serotonin subtype 3 receptor antagonists are at least as effective as standard antiemetics but with a better side effect profile.

**Endocrine Therapy for Breast Cancer**

Agents that block estrogen receptors or reduce estrogen synthesis have been used as palliative treatments for breast cancers in postmenopausal women. Since the late 1970s, the estrogen receptor blocker tamoxifen has been the standard first-line treatment, because it was shown to be as effective as other treatments used at the time but with fewer side effects (see Bonneterre, 2000 for references). Additional innovation is needed for breast cancer therapy, however, since resistance to tamoxifen develops, and disease recurrence or progression during tamoxifen therapy is common. Despite good tolerability, long-term use is associated with an increased risk of endometrial cancer (see Nabholtz, 2000 for references).

The aromatase inhibitor drugs, which block estrogen synthesis, have been used in breast cancer treatment since the early 1980s. But these drugs also have
shortcomings, since they have either weak action or non-specific effects on enzymes involved with other hormones and are frequently associated with substantial toxicity (Miller, 2000). Recently, several new-generation aromatase inhibitors have been developed that are far more specific and more powerful in their mechanism of action than their predecessors.

The new-generation aromatase inhibitors anastrozole and letrozole rival tamoxifen in their clinical benefit and toxicity profile in these patients (Dowsett & Lonning, 1997; Dombernowsky et al., 1998; Nabholtz et al., 2000; Bonneterre et al., 2000). Anastrozole appears to have a particularly low incidence of gastrointestinal side effects and has been reported to cause fewer thromboembolic events and vaginal bleeding episodes than tamoxifen (Nabholtz et al., 2000; Bonneterre et al., 2000). Similarly, letrozole also may outperform tamoxifen in the first-line treatment of advanced metastatic breast cancer and is under priority review by the FDA for this indication.

V. INCREMENTAL INNOVATION IN THE FUTURE

The advent and wide use of several new drug discovery methods (i.e., computer-aided drug design and combinatorial chemistry linked to high-throughput screening) suggest that approaches to innovation based on molecules with known clinical actions might become less important in the future. However, some observers have noted that these new methods have not yet lived up to their promise in replacing the old techniques (Horrobin, 2000; Lahana, 1999; Loftus, 1994). Thus, it is likely that incremental improvement of existing therapies will continue to remain an important source of new drugs. New knowledge derived from the fields of biotechnology and genetics will aid the innovation process.

**Biotechnology**

Medicines derived from biotechnology are a relatively new addition to the pharmacopoeia. However, we are already beginning to see some important incremental improvements in these agents in the form of improved formulations.

In December 1999, Amgen filed for FDA approval of a novel erythropoiesis-stimulating protein for anemia in patients with chronic renal failure and chronic renal insufficiency. This agent, darbepoetin alfa (Aranesp), is similar to the protein drug epoetin-alpha (Epoegen), which stimulates red blood cell formation and is indicated for anemia related to renal insufficiency, HIV/AIDS therapy, and cancer chemotherapy. Aranesp has a longer half-life and will
likely allow for less-frequent dosing (Macdougall, 1999). Aranesp enables the management of hemoglobin levels with one dose a week or, in some cases, one dose every 2 weeks, as opposed to three doses a week for Epogen (Pihl-Carey, 1999).

Genentech has introduced TNKase, a new “clot buster” (tissue plasminogen activator) used in the treatment of heart attacks. TNKase is the first thrombolytic agent that can be administered as a single injection, enhancing its potential usefulness in emergency and transport situations and in other scenarios outside the hospital setting. Additional advantages of single-bolus dosing include the ease of storage, reconstitution, and administration of the drug for health care providers who work in intense and emergent patient environments. These benefits improve access to therapy for heart attack patients. Single-bolus thrombolytic therapy also should result in fewer dosing errors (McCann, 1999).

Genetic Variation and Individualized Therapy

Knowledge from pharmacogenetics, the new and rapidly expanding study of genetically determined variations in drug response, may soon help in the selection of optimal, individualized therapy from agents that are similar but have somewhat different actions at drug receptors or enzymes. Many diseases are now believed to represent clusters of different defects in the genes responsible for the structure and function of receptors and other proteins. It has been estimated that an average of 5 to 10 genes contribute to a multifactorial disease (Drews, 2000). This may explain why a drug that acts at one specific defect is not effective in all individuals with that disease.

For example, the clinical response rate for the atypical antipsychotic drug clozapine varies between 30% and 60%, part of which reflects variation (polymorphism) in genes governing neurotransmitter-receptor-drug relations. Among a broad population of schizophrenic patients, an optimal combination of six gene polymorphisms, across multiple genes, has been associated with a 77% success rate in predicting a response to clozapine (Arranz et al., 2000). Since other atypical antipsychotic agents such as risperidone and olanzapine differ from clozapine in their affinities for D4, muscarinic, 5-HT1A, 5-HT6, and 5-HT7 receptors, it is possible that these agents may be more effective in schizophrenic patients with other polymorphism combinations.

Similarly, variation in a gene related to metabolism of high-density lipoprotein affects the ability of the drug pravastatin to lower cholesterol (Kuivenhoven et al., 1998). Pravastatin failed to lower cholesterol in the 16% of the study population who had the gene variant associated with this polymorphism.
The discovery of genetic polymorphisms of receptors associated with asthma may enable the development of specific drugs for patients with genetic subtypes of this disease. Beta-2 receptor agonist drugs cause bronchodilation and are mainstays in asthma treatment, and beta-2 receptor polymorphisms contribute to the variable response to these agents. Eventually drugs may be designed for individuals based on their beta-2 receptor genotype. This would help physicians tailor asthma therapy beyond current guidelines for care (Elliott, 2000).

VI. ECONOMIC VALUE OF INCREMENTAL INNOVATIONS

Newer agents of a class, or new formulations of existing agents, often enable new cost-effective uses or more efficient treatment for the original indication. Incremental pharmaceutical innovations can reduce costs for health care providers and insurers and in some cases can improve employee productivity. Savings can come from reduced overall treatment costs due to shortened or eliminated hospital stays, less need for surgery, and increased worker efficiency and less absenteeism.

*Overall Cost Savings With Controlled-Release Formulations*

Controlled-release (CR) dosage forms often provide improved efficacy, safety, or compliance benefits, as well as economic value. The clinical importance of CR dosage forms for some diseases can be dramatic. In the management of hypertension, once-daily dosing that provides 24-hour efficacy protects against the risk of sudden death, heart attack, and stroke caused by the abrupt rise in blood pressure after one arises from overnight sleep (Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, 1997).

Cramer and Saks (1994) have reviewed studies on the clinical and economic benefits of CR formulations. Their review generally found the price of CR formulations to be higher than that of conventional formulations, but substantial cost offsets were commonly reported. The following is a summary of Cramer and Saks’ findings.

*Cardiovascular therapy.* In cases where compliance was superior, the higher costs of sustained-release verapamil were more than offset by lower physician, hospital, and laboratory expenditures. Similarly, patients receiving sustained-release diltiazem had better prescription refill compliance and significantly lower aggregate health care costs.
Controlled-release nifedipine simplifies the dosage regimen to once daily, are approved for the additional indications of hypertension and angina, and reduces adverse effects from vascular dilation. Therapy with transdermal clonidine, given once weekly (compared with a twice-daily oral formulation), was associated with improved compliance, fewer adverse effects from blood level peaks, and lower nondrug health costs (e.g. physician, hospital, and laboratory costs). Overall costs of care with once-daily oral formulations of various antihypertensives were found to be lower than those of formulations requiring more frequent dosing, suggesting that the cost savings from both oral and transdermal CR dosage forms are related to improved compliance.

The deterioration in the sense of well-being caused by the sharp peaking of blood levels associated with conventional formulations of the beta-blocker metoprolol did not occur with CR metoprolol.

**Pain management.** Controlled-release oral morphine and transdermal fentanyl have higher acquisition costs compared with short-acting or injectable agents, but lower total administration costs may offset the higher purchase price. These long-acting products also address many pain management problems, including inadequate or mistimed dosage, labor costs, patient acceptance, and adverse effects on quality of life. Controlled-release oral morphine is taken twice daily. Transdermal fentanyl is administered every 3 days and can be used by patients unable to take oral medication.

In summary, some CR dosage forms add economic value by simplifying administration regimens, thereby enhancing compliance. By modulating drug input, CR formulations prevent supertherapeutic or subtherapeutic plasma drug concentrations. The resultant improvements in efficacy, adverse effect profile, and quality of life can decrease both the costs associated with diagnosing and treating drug toxicity and the need for costly reevaluation to adjust dose, change medications, or escalate therapy (Cramer & Saks, 1994).

**Overall Cost Savings with Newer ACE Inhibitors**

Small et al. (1997) compared total costs and adherence to the regimen for older versus newer ACE inhibitors in the treatment of over 6000 elderly patients with hypertension. Total cost of therapy included acquisition costs for the ACE inhibitors and concurrent antihypertensive agents, and nondrug costs including laboratory tests, hospitalization, and clinic visits. Total median cost per month was greater for older than for newer agents: $60 vs. $53. The mean percentage of patients complying with therapy as determined by refill data was greater with newer than with older agents: 66% vs. 58%.
Hospital Cost Savings with Low-Molecular-Weight Heparins

The low-molecular-weight (LMW) heparins, introduced in the United States in the 1990s, are smaller pieces of the heparin molecule and represent a major therapeutic and economic advance over unfractionated heparin in the treatment and prevention of coagulation disorders. They can be administered once daily by subcutaneous injection in a weight-adjusted dose without subsequent monitoring or dose adjustment.

A major use of the LMW heparins is for treatment and prevention of deep venous thrombosis (DVT) after surgery. Deep venous thrombosis is associated with more than 600,000 hospitalizations annually in the United States and results in more than 200,000 deaths caused by pulmonary embolism (Howard, 1997). Patients with acute DVT have traditionally been hospitalized and treated with a continuous infusion of unfractionated heparin for 5 to 10 days, followed by oral anticoagulation therapy on an outpatient basis. The wide variability in anticoagulant response among patients treated with unfractionated heparin requires frequent monitoring and dosage adjustments to keep anticoagulation in the therapeutic range. For most patients who have no major risk factors for bleeding or subsequent pulmonary embolism, hospitalization is necessary only for monitoring purposes (Yeager & Matheny, 1999).

Low-molecular-weight heparins are derived from depolymerization of standard heparin, which yields fragments approximately one third the size of the parent compound. Compared with unfractionated heparin, LMW heparins have greater bioavailability and little interpatient and intrapatient variability in response to a given dosage (Haines & Bussey, 1995).

Each of the seven available LMW heparins is prepared using a different method of depolymerization, resulting in distinct molecular weights and different relative effects on clotting factors. For this reason, LMW heparins are unique and not necessarily therapeutically interchangeable, although their pharmacological and clinical characteristics are similar (Hirsh et al., 1995).

Low-molecular-weight heparins are at least as safe and effective as unfractionated heparin in the treatment of DVT (see Yeager & Matheny, 1999), and are associated with less bleeding and fewer episodes of heparin-induced thrombocytopenia. Their longer half-life and more predictable anticoagulant response enable subcutaneous administration without laboratory monitoring. Thus, the use of LMW heparins can shift the management of DVT to the ambulatory setting. This enables significant cost savings by preventing or shortening hospitalization and by increasing patient comfort and satisfaction with health care (Heaton & Pearce, 1995).
Patients receiving LMW heparin reported a higher quality of life in terms of physical and social function and sense of well-being. Treatment of DVT with LMW heparin was more cost-effective than therapy with unfractionated heparin because the hospital stay was 60% to 70% shorter without an increase in the cost of home health care (Koopman et al., 1996; Levine et al., 1996). Furthermore, social functioning and physical activity were better in the group receiving LMW heparin (Koopman et al., 1996).

Economic appraisals of DVT therapy with LMW heparins compared with unfractionated heparin have shown a 20% reduction in disease management costs attributable to decreased length of hospital stay and an average cost savings of over $900 per patient (Heaton & Pearce, 1995; Hull et al., 1997). Elimination of even a single hospital day by use of LMW heparin would likely yield a savings, based on a drug cost of less than $200 per day. Rydberg et al. (1999) reported that the average cost of treating a patient with uncomplicated DVT was reduced by $5000 to $8000 when LMW heparin was used instead of standard heparin therapy.

**Hospital Cost Savings with New-Generation Diuretic**

Health care costs for patients with CHF randomly assigned to treatment with the original loop diuretic furosemide were compared with costs for patients assigned to treatment with a newer loop diuretic, torasemide (Stroupe et al., 2000). Furosemide differs from torasemide in that absorption of the former is less complete and more variable, and this is correlated with a highly variable clinical response (Murray et al., 1997) with potentially important effects on patient outcomes. Torasemide is more expensive; its annual per patient acquisition cost in this study was $518 higher than that of furosemide. But the group of patients taking torasemide experienced fewer hospitalizations (18% vs. 34% for CHF admissions, and 38% vs. 58% for admissions with any cardiovascular disease). This translated to a net savings in hospital costs of $536 for CHF admissions and $1027 for all cardiovascular admissions. The authors projected a net annual savings in hospital costs of $700,000 for CHF admissions and $1.3 million for all cardiovascular events if torasemide was used instead of furosemide for all CHF patients at their hospital.

However, outpatient costs and total costs did not differ between treatment groups in this study regardless of whether drug costs were considered. The poor health status of these patients and the resulting need for a variety of health care services unrelated to cardiovascular causes were believed to have contributed to the failure to find a significant difference in outpatient and total costs (Stroupe et al., 2000).
Hospital Cost Savings with Newer Cephalosporin Antibiotics

Third-generation cephalosporins, developed as a result of molecular modification, may in some situations produce greater savings than earlier cephalosporins. Mandell-Brown et al. (1984) examined the effectiveness and costs associated with earlier versus third-generation agents in preventing infection after head and neck surgery. Thirty-three percent of patients given an earlier agent developed infections versus 10% given third-generation agents. The extra costs resulting from the suboptimal effects associated with the earlier agent were extrapolated to a group of 100 patients. The cost of prolonged hospitalization caused by 24 additional infections associated with the earlier agent was $251,210.

Incremental advances have resulted in cephalosporin antibiotics requiring intravenous administration only once daily instead of three or four times a day. Such agents have been shown to save money by reducing the time required for hospital personnel to set up intravenous infusions and monitor drug administration. National savings in hospital costs have been estimated at $85 to $115 million per year (Eisenberg et al., 1984).

Some cephalosporin antibiotics are now being used for home intravenous infusion in the treatment of conditions such as osteomyelitis, endocarditis, wound infections, urinary tract infections, and septic arthritis. Home therapy with these agents saves hospital admission costs and reduces income loss for those patients able to work while receiving therapy. Incremental improvements have produced cephalosporins suitable for home use (i.e. those having low toxicity, a broad spectrum of action, and, especially, a long duration of action allowing for less-frequent dosing).

Treatment of joint infections with a long-acting agent (cefonicid) enabled 12 of 15 patients to complete therapy on an outpatient basis. These patients avoided 390 hospital days, saving $64,000, and also saved $10,000 in lost work income (Kunkel & Iannini, 1984). A similar study of 79 patients comparing home-injected vs. hospital use of ceftriaxone, another long-acting injectable agent, showed an average saving of over $6000 per patient and a benefit/cost ratio of 5:1 (Portez et al., 1984).

Cost Savings with Beta-Blockers

Timolol

Timolol, a beta-blocker derived from molecular modification of existing beta-blocker agents, has been shown to be cost-effective in treating glaucoma and in preventing second heart attacks (A.D. Little Inc., 1982a, b).
The extended use of timolol in the treatment of glaucoma is made possible through the development of a topical dosage form enabling direct application to the eye. Timolol is significantly more cost-effective than surgery in treating glaucoma. The annual benefit of using the drug for the entire eligible population was estimated to range from $750 million to $1.1 billion. That benefit exceeded the annual costs of timolol by a factor ranging from 8:1 to 13:1.

Timolol can prevent death due to second heart attacks, potentially for 27.5% of all patients surviving an initial heart attack (approximately 10,000 persons a year). Timolol is also able to reduce the incidence of nonfatal second heart attacks by 16.0%. The annual benefit for the entire eligible population was calculated to range from $1.6 to $3.0 billion. Benefits exceeded costs by a factor ranging from 8:1 to 14:1. The use of timolol slightly increases the direct treatment costs of preventing second heart attacks, but this is more than offset by a gain in patient productivity. The net result is a saving of $4000 to $7000 per patient per year.

Metoprolol
Metoprolol, another beta-blocker developed through molecular modification, is also effective in prolonging life and improving the quality of life after a heart attack (Olsson et al., 1987). More patients receiving metoprolol returned to work within 3 months after their heart attack compared with those who did not receive the drug. The number of rehospitalizations was also lower for patients taking this drug. The cost of treatment was greatly offset by savings from fewer hospitalizations and from the patient’s earlier return to work. The treatment cost per patient during a 3-year period was reduced by $2400 (Olsson et al., 1987).

Carvedilol
The third generation beta-blocker carvedilol, which has a wide spectrum of pharmacological effects (it blocks beta-1, beta-2, and alpha-adrenergic receptors, as well as having antioxidant properties), has recently shown to be effective in patients with severe heart failure (Packer, 2000). Although carvedilol slows heart rate, it improves left ventricular function, allowing the heart to pump more blood. Carvedilol had previously been found to be effective in patients with mild to moderate heart failure, but was believed to be ineffective in more severe cases because it decreases heart rate and contractility. However, the Copernicus Study showed that severe heart failure patients treated with carvedilol, along with other therapy for this condition (diuretics, ACE inhibitors, digitalis), had a 35% lower mortality risk compared with patients treated with conventional therapy only. This should be of great clinical and economic importance since an estimated 750,000 to 1 million Americans suffer from severe heart failure. The drug could save an estimated 50,000 lives a year among these patients.
Improved Productivity with Non-sedating Antihistamines

Seasonal allergic rhinitis (hay fever) affects an estimated 13 million working adults and causes absenteeism and diminished work productivity (Fireman, 1997). Estimates of at-work productivity losses range from $2.4 to $4.6 billion (Crystal-Peters et al., 2000), much of which comes not from absence due to allergies but from lost productivity due to the sedating effects of the older medications used to treat it.

The American Academy of Allergy, Asthma and Immunology indicates that when patients self-manage allergic rhinitis with first-generation, sedating antihistamines, lost productivity and missed workdays add $3.8 billion yearly to indirect costs. A poll by Louis Harris & Associates for USA Today (August 7, 1999) found that over half of adults reported suffering from a related disorder, sinus problems; 34% of sufferers said the condition affects work performance.

The first-generation and some second-generation antihistamine preparations used for these conditions cause sedation, variously described as drowsiness, fatigue, and altered cognitive and psychomotor function. The new non-sedating antihistamines avoid these central nervous system side effects, since they do not cross the blood-brain barrier.

Compared with non-sedating agents, sedating antihistamines have been linked to more workplace accidents and injuries (Fireman, 1997) as well as to impaired work performance (Cockburn et al., 1999a, b). A study of productivity in clerical workers (insurance claims processors) with allergies found that the productivity of workers using sedating antihistamines was 13% lower than the productivity of workers using non-sedating antihistamines (Cockburn et al., 1999a). The value of lost output for the employer was calculated at $9.00 daily for each employee taking sedating histamines. Assuming a greater daily cost of up to $1.50 for non-sedating antihistamines, this translates to a favorable cost/benefit ratio (Cockburn et al., 1999b).

Similarly, the William M. Mercer employee benefits consultant company used an actuarial model to calculate that many employers can realize a net financial gain of $2 to $4 for every $1 spent when allergy sufferers use non-sedating instead of sedating treatments (William M. Mercer, 2000). The savings result from a combination of productivity gain, fewer accidents and disability claims, and less sick leave.

Improved Cancer Drugs

Cisplatin is a cancer chemotherapeutic agent that is particularly effective in the treatment of testicular and ovarian cancer. Carboplatin is an analog of cisplatin,
created through molecular manipulation. It has a similar spectrum of antitumor activity. However, it has a more favorable toxicity profile, is easier to administer, and is associated with improved quality of life in cancer patients (Tighe & Goodman, 1988). Carboplatin has the particular advantage of not requiring intensive (intravenous) hydration before and after administration to avoid kidney toxicity. This enables the agent to be given on an outpatient basis, thereby saving the cost of hospitalization. As a result, although carboplatin is about 10 times more expensive than cisplatin, the overall costs of treatment are about one third less (Tighe & Goodman, 1988).

Despite their positive activities in a variety of cancers, cisplatin and carboplatin are both ineffective in colorectal cancer, the second-leading cause of death in North America, claiming 56,000 lives annually. But a third anticancer platinum compound, oxaliplatin, has shown promising activity in advanced colorectal cancer when given alone or in combination with other chemotherapies, even in patients refractory to standard agents (Giacchetti et al., 2000; de Gramont et al., 2000). Even small improvements in colorectal cancer treatment outcomes can have potentially large economic benefits, although these have not yet been quantified.

Second-Generation Diabetes Drugs: Improved Glycemic Control Without Increased Costs

Second-generation sulfonylurea agents used in the treatment of diabetes have several advantages over the first-generation agents in this class (see Sulfonylurea Agents, above). In 1987 California added the second-generation agents to the Medi-Cal formulary, thereby allowing Medicaid recipients to receive these drugs. A study of more than 5000 Medi-Cal patients determined the clinical and economic effects of this addition after 6 months (Sclar et al., 1990). Addition of the new agents was correlated with an overall improvement in the outcome of drug therapy and a corresponding decrease in hospital and nursing home costs for diabetic patients. However, drug expenditures rose for patients prescribed the new agents, since these drugs are more expensive than the first-generation agents. As a result, total expenditures were unchanged. Although overall costs were not reduced, the addition of these incremental improvements resulted in a higher level of glycemic control without increasing costs.

VII. POLICY IMPLICATIONS

Public policies or business strategies resulting in intentional or de facto restriction of the availability of incremental pharmaceutical innovations can have negative
implications for health care cost containment and for research investment in new pharmaceuticals. Failure to recognize the uniqueness of incremental innovations when devising cost-containment strategies may ultimately be self-defeating.

Cost Containment

The availability of multiple medications within a class can be expected to increase competition on price among agents within the class. This is true for almost all goods and services, not just pharmaceuticals. Since incremental innovations must compete with their predecessors for market share, they are often priced at a discount. DiMasi (2000) has shown that new drugs in a class are often priced lower than existing agents within that class. DiMasi examined the pricing of new entrants to drug classes and subclasses in eight therapeutic categories: antiarthritics, antidepressants, antihistamines, antihyperlipidemics, antihypertensives, antiulcer agents, and two antibiotic classes (cephalosporins and macrolides). These classes accounted for half of total retail prescription drug expenditures in 1999.

The majority of new drugs were found to be launched at discounts (sometimes substantial) relative to both the class price leader and to the average price in the class (Table 4). Of the 20 drugs examined, 13 were priced at discounts of at least 5%. Five of the drugs were introduced essentially at parity with existing prices (four of them were angiotensin-receptor blockers). The fifth drug was the COX-2 inhibitor rofecoxib, which entered the market at the same price as celecoxib, the first COX-2 inhibitor to be launched. Only the third-generation oral cephalosporins entered the market at a premium, but they are still discounted relative to the price leader.

Investment in Research and Development

Price controls or other restraints on the marketing of incremental innovations could eventually change the R&D process and accelerate ongoing alterations in the structure of the pharmaceutical industry. Although patent laws encourage innovation by protecting a new product’s market, restrictive policies diminish the advantage of patent exclusivity by encouraging or forcing the use of alternate medications. This could reduce industry’s incentive to produce incremental improvements. In addition, overall R&D investment by pharmaceutical companies, in both incremental and breakthrough innovations, could decrease. The reasons are twofold.

The first reason involves the importance of incremental innovation to a company’s revenue stream. No mature industry can sustain itself on income
from breakthrough innovation alone. The pharmaceutical industry must generate revenue based predominantly on incremental innovations, which characterize the majority of products and contribute the majority of revenue. This revenue pattern is typical of other mature high-technology industries. If these products are precluded from the marketplace by restrictive policies, revenues will decline.

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

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

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 A positive value indicates a lower price for the new entrant, while a negative value indicates a higher price.
sharply and fewer resources may be available to invest in R&D – either for incremental or breakthrough products.

The second reason why R&D investment is likely to decrease significantly in the face of restrictive policies involves the management of risk. Any technology portfolio contains a mix of projects of differing risk. The lower risk projects (i.e., those with a relatively better chance of reaching the marketplace) are generally incremental innovations, not blockbusters. The pharmaceutical industry is less likely to invest research resources in such products if they are doomed by restrictive policies to commercial failure. The resources not spent on the lower risk projects will not, in most cases, be shifted to higher risk projects with a small chance of success in reaching the marketplace. Industry research investments are huge risks, which must be managed prudently on behalf of the stockholders; to wager all on just the high-risk projects would mean commercial failure in many cases.

In an environment of price controls and other constraints on the marketing of incremental innovations, pharmaceutical companies could be confronted with a difficult choice: to continue channeling research investment into incremental advances that may no longer be marketable or to redirect resources and spend even more on radical improvements that are marketable, but have little chance of success. Faced with such a dilemma, many companies may scale back on R&D; others may change the mix within their portfolios of drugs in development. Portfolios will become less diversified, with less emphasis on products having an incremental advantage and greater emphasis on more risky projects. Smaller companies, lacking the capital to participate in the long-odds, high-stakes strategy of developing breakthroughs, may be forced to terminate research. Other companies, after a period of strategic reorganization and resource redirection, may eventually conclude that R&D, previously risky, is now too risky to continue.

Pharmaceutical product development often takes 10 or more years, during which time similar products may reach the market, turning a breakthrough prospect into a similar version of another company’s drug. According to Peck and Rabin (1990), “If these second or third versions are kept from the market, many pharmaceutical companies may not be able to support continued research. Nobody knows whether innovation could continue in an environment where the risk of failure gets raised higher in this way.”

Experience indicates that the pace of pharmaceutical innovation is sensitive to a negative marketplace environment. In the past, the increased risk of financial losses created by lawsuits probably slowed innovation in the areas of vaccines and contraceptives (Peck & Rabin, 1990). The mere threat of price controls can dampen enthusiasm for investment. In the spring of 1994, discussion of the possibility of price controls for innovative products by the Clinton health care
task force caused 13 of 16 fledgling biotechnology companies to withdraw their initial public offerings of stock and their efforts to go public (Abrams, 2000).

Reduction in incremental innovation could also result in increased drug prices. If only breakthrough drugs are able to reach the market, many companies will be unable to recoup their overall R&D investments. Accordingly, prices charged for those breakthroughs will have to be the sole support for both research and profits (Peck & Rabin, 1990).

Professors Henry Grabowski and John Vernon of Duke University estimated the negative effects of restrictive policies on revenues and innovation in the pharmaceutical industry (Grabowski & Vernon, 1994; 1996; 2000). They divided drugs into 10 categories based on sales revenues and found that only the 3 top-revenue categories returned the average investment in bringing a new drug to market; the rest lost money. Grabowski and Vernon argue that since the products in the top category make a tempting target for cost-containment efforts, total revenues would be severely reduced. They continue: “With such large loses on the (average) new drug introduction, firms would be expected to respond by curtail-ing expenditures on future R&D projects . . .” (Grabowski & Vernon, 1996, 203). These cutbacks may negatively impact research on incremental innovations as well as breakthrough products, since many of the drugs in the top revenue category are not the first ones in their respective classes (Grabowski & Vernon, 2000).

VIII. CONCLUSIONS

Pharmaceutical development is a process whereby older therapies are continually replaced by newer therapies offering incremental advantages. This evolutionary process may not be apparent in a “snapshot” of the collection of drugs available at a given point in time. From such a static viewpoint, incremental innovations can be perceived as duplicative, profit-driven imitations of successful drugs. However, this perspective distorts the true nature of the pharmaceutical R&D process. Over time, incremental innovation has resulted in striking improvements in existing drug therapy and patient care, and in some cases in reduced total costs for therapy.

Barriers to the marketing of incremental innovations could slow down the march of small but significant therapeutic advances and undermine the incentives for competitive research. Such policies would interfere with the fundamental process of medical advancement at crucial time in pharmaceutical development. We have entered a period of great promise in biotechnology and genomics, with the potential for effective, individualized treatment or cures for major diseases.

It is unlikely that such barriers will shut down pharmaceutical R&D or cause the demise of healthy companies. The scenario above is subject to many forces
that will either accentuate or blunt its impact. The point is that the future of public health, as advanced through pharmaceutical innovation, is being threatened by short-term attempts to contain current costs. What is most disturbing is that we will never know the true opportunity costs incurred, or the pharmaceutical innovations that never were.

One thing is certain: the richness of variability within therapeutic classes will be diminished if restrictive policies progressively reduce the number of marketed compounds. This would move us in the direction of less differentiated therapeutics, where the average patient will be treated with the average drug. Patients with more specific needs will not receive individualized treatment because more selective pharmaceutical therapies will not exist.

Policy makers need to grapple with the risks as well as the benefits associated with cost-containment tactics that limit the availability of pharmaceutical innovations. This paper has focused on a major risk that is generally not considered – the inhibition of small but ultimately vital advances in pharmaceutical technology. Since drug therapy is generally agreed to be the most cost-effective treatment modality, the economic stakes are high.

NOTES

1. Major innovations are generally defined here as the first agents with a particular clinical action (e.g. antihypertensives) or pharmacological action (e.g. beta-blockers) or the first with the same clinical effect as existing agents but with a different mechanism of pharmacological action (e.g. diuretics vs. beta-blockers).

Incremental innovations are follow-on modifications in molecular structure or dosage formulation having a similar, but not identical, pharmacological action (e.g. beta-1 selective beta-blockers vs. non-selective beta-blockers) or a different absorption, metabolism, or excretion profile (e.g. sustained action).

Agents are often referred to as second-, third-, or even fourth-generation products, but there is no uniform criterion for this label. Subsequent generations may represent either major or incremental innovations. The second-generation or higher drugs discussed in this report all are considered to be incremental innovations.

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Too Many Drugs?


Too Many Drugs?

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