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More New Drugs

New drug approvals of 2000

Introduction

Again last year the FDA approved dozens of new drug and new dosage forms, including 27 new molecular entities, and again health care professionals find themselves sifting and winnowing to separate pharmaceutical advances from marketing innovations. Again, the price of prescription drugs is a topic frequently revisited by the media even after major coverage subsided following the 2000 election campaign. The New York Times recently reported that last year, spending on prescription drugs increased by 18.8% to \$131.9 billion dollars.¹ This rate of increase has been steady since 1999, and the National Institute for Health care Management Foundation estimates that patients and institutional payers are spending 40% more on drugs than they did in 1998. According to the Times' interpretation of the Foundation report, three factors have driven up prices. Forty-two per cent of the increase resulted from an increased number of prescriptions written and filled, 36% from a shift to more expensive drugs, and 22% from the drug price increases as such. The top 50 drugs represented 30% of all prescriptions. Their average price was \$67.15 compared to \$36 for the other medications. These include many of the most aggressively marketed newer drugs whose names are now household words because of direct consumer advertising. The study summed up the situation simply: "Americans are demanding, and physicians are prescribing, a higher volume of medicines."

The increase in sales of five drugs accounted for one-fifth of the entire increase: rofecoxib (Vioxx®), lansoprazole (Prevacid®), atorvastatin (Lipitor®), celecoxib (Celebrex®), and metformin (Glucophage®).¹ The best-selling category was antidepressants, including citalopram (Celexa®).

Approvals in 2000

New molecular entities approved in 2000 are listed in Table 1. Table 2 contains a selection of new dosage forms approved last year, while Table 3 lists the four medications withdrawn from the market.

Do the new approvals represent substantial advances in patient care? Table 4 categorizes these medications according to their therapeutic applications. At a glance, the largest category includes drugs used mostly in specialty practices like interventional cardiology, neurology or ophthalmology. For example, insulin glargine (Lantus® - Aventis) is a new, long-

acting insulin that may compete with ultralente insulin. It will be used primarily by the subset of Type 1 diabetes patients who need a steady 24-hour basal level of insulin that can be supplemented by at least three mealtime injections of regular insulin for tight glucose control. Endocrinologists rather than family physicians currently manage most of these patients. Pharmacists dispensing Lantus® should remind patients that this long-acting insulin should appear clear, not cloudy, in the vial.

The second-largest category in Table 4 comprises the me-too drugs, variations on chemical classes already in clinical use. These range from two new eyedrops for glaucoma to yet another proton-pump inhibitor. Most of these entries have either huge or lucrative potential markets, so that even modest market share translates to profitability. Lifestyle enhancers include a facial hair growth inhibitor, a cholinergic agent that relieves dry mouth in patients with Sjogren's Syndrome, and a prophylactic agent for chloroquine-resistant malaria that will be used mostly by well-to-do tourists, not inhabitants in endemic areas. Stopgap drugs are partially effective medications targeted to conditions that affect large numbers of people, but only have limited therapeutic potential. Rivastigmine (Exelon®), like donepezil (Aricept®) and galantamine (Reminyl®) may produce a modest improvement in some Alzheimer's patients, but for most, it functions more like a stabilizer to slow the rate of cognitive decline and delay the necessity for nursing home placement.²

Therapeutic Advances

1. Pneumococcal 7-valent conjugated vaccine (Prevnar®)

Before 1990, when the conjugate *Haemophilus b* vaccines were introduced, *H influenzae* was the leading cause of invasive bacterial disease, including bacterial meningitis, in infants and young children.³ Now that the conjugate vaccines are in routine use, *H influenzae* type b invasive disease has been virtually eliminated in the United States. Since 1995, pneumococci have become the principal cause of invasive bacterial disease in children under five years old. In these children, the most common presentation of pneumococcal infection is not meningitis, but bacteremia without a focus of infection. Because polysaccharide vaccines have limited immunogenicity in children under two years of age, protection against pneumococcal infection was not available until a vaccine chemically bonded to more immunogenic proteins could be developed.

The information given and views expressed herein do not necessarily reflect the opinions of PSW, its Board or members.

Table 1. New Drug Approvals in 2000

Treatment Area	Drug	Trade_Name	Manufacturer	Indication/ Action
Arthritis	meloxicam	Mobic	Boehringer-Ingelheim/ Abbott	Osteoarthritis
	cevimeline	Evoxac	SnowBrand	Sjogren's dry mouth
Cancer	arsenic trioxide*	Trisenox	Cell Therapeutics	Acute promyelocytic leukemia
	gentuzumab ozogamicin*	Mylotarg	Wyeth-Ayerst	AML in first relapse
	triptorelin pamoate	Trelstar Depot	Debio Recherche Pharmaceutique	Advanced prostate Ca
Cardiovascular	argatroban	Acova	Texas Biotechnology	Anticoagulant for HIT
	bivalirudin	Angiomax	The Medicines Company	PTCA in unstable angina
	colesevelam	Welchol	GelTex	Hypercholesterolemia
	tenecteplase	TNKase	Genentech	AMI thrombolysis
	tinzaparin	Innohep	DuPont	DVT treatment
Chemical Terrorism	skin exposure reduction paste against chemical warfare agents SERPACWA	Skin Exposure Reduction Paste Against Chemical Warfare Agents	US Army Medical Research And Material Command	Prevention of exposure to chemical agents
Dental	articaine/ epinephrine	Septocaine	Deproco	Local dental anesthetic
Dermatology	eflornithine cream 13.9%	Vaniqa	Bristol-Myers Squibb	Facial hair removal
Endocrine	insulin aspart	NovoLog	NovoNordisk	Diabetes mellitus\
	insulin glargine	Lantus	Aventis	Diabetes mellitus
	nateglinide	Starlix	Novartis	Type 2 diabetes
Eye	unoprostone isopropyl	Rescula	CibaVision	Glaucoma
	levobetaxolol 0.5% ophth	Betaxon	Alcon	Glaucoma
	verteporfin for injection	Visudyne	CIBA Vision	Macular degeneration
G-I	alosetron	Lotronex	Glaxo Wellcome	IBS in women
	balsalazide	Colazal	Salix	Ulcerative colitis
	pantoprazole	Protonix	Wyeth-Ayerst	Erosive esophagitis
Infectious Disease	atovaquone/ proguanil	Malarone	Glaxo Wellcome	Malaria prevention
	docosanol cream 10% (OTC)	Abreva	Avanir Pharmaceuticals	Oral-facial herpes simplex
	linezolid	Zyvox	Pharmacia Upjohn	VRE, MRSA pneumonia
	lopinavir/ ritonavir	Kaletra	Abbott	Protease inhibitor
Neurology	oxcarbazepine	Trileptal	Novartis	Partial seizures
	rivastigmine	Exelon	Novartis	Alzheimer's
	zonisamide	Zonegran	Elan	Partial seizures
Reproductive	cetorelix acetate	Cetrotide	ASTA Medica	Prevention of LH surges (IVF)
	mifepristone	Mifeprex	Danco Labs	Pregnancy termination
Vaccines	pneumococcal 7-valent conjugate vaccine	Prevnar	Wyeth Lederle	Invasive pneumococcal disease

* denotes orphan drug

Table 2. Selected New Dosage Forms in 2000

Treatment Area	Drug	Trade Name	Manufacturer	Indication/Action
Contraception	levonorgestrel IUD	Mirena	Berlex	5-year contraceptive
	medroxyprogesterone acetate/ estradiol cypionate	Lunelle	Pharmacia/Upjohn	Monthly IM contraceptive
Dermatology	diclofenac sodium 3%	Solaraze	SkyePharma, Inc	Actinic keratoses
	tacrolimus ointment 0.1%, 0.03%	Protopic	Fujisawa	Eczema
Endocrine	metformin/glyburide	Glucovance	Bristol-Myers Squibb	Type 2 diabetes
Eye	azelastine ophth sol'n 0.05%	Optivar	Muro Asta Medica	Allergic conjunctivitis
	levofloxacin ophth sol'n 0.5%	Quixin	Santen	Anti-infective
	nedocromil ophth sol'n 2%	Alocril	Allergan	Allergic conjunctivitis
Infectious Disease	lamivudine/ zidovudine/abacavir	Trizivir	Glaxo Wellcome	HIV infection
Neurology	botulism toxin type B	Myobloc	Elan Corporation	Cervical dystonia
Pulmonary	caffeine citrate*	Cafcit	Boehringer Ingelheim	Apnea of prematurity
	fluticasone propionate/ salmeterol powder	Advair Diskus	Glaxo Wellcome	Asthma (maintenance)
	budesonide inhalation suspension	Pulmicort Respules	AstraZeneca	Pediatric asthma (maintenance)

Table 3. Drug Withdrawals in 2000

Drug (Brand) Mfr	Adverse Effect
Alosetron (Lotronex®) Glaxo Wellcome	Ischemic colitis
Cisapride (Propulsid®) Janssen	Arrhythmias from drug interactions, pre-existing cardiac conditions
Troglitazone (Rezulin®) Parke-Davis	Liver toxicity
Phenylpropanolamine	Risk for hemorrhagic stroke, especially when used as appetite suppressant

Table 4. Year 2000 Approvals Categorized by Therapeutic Potential

Therapeutic Advance	Specialty Practice		Stopgap	Lifestyle	Me-Too
Prevnar ^B	Acova	NovoLog	Abreva	Evoxac	Betaxon
Trileptal	Angiomax	Septocaine	Exelon	Malarone	Colazal
Visudyne	Cetrotide	Starlix	Lotronex	Vaniqa	Innohep
Zyvox	Kaletra	TNKase ^B			Mobic
Solaraze	Lantus	Trelstar			Protonix
Trizivir	Lotronex	Trisenox*			Rescula
	Mifeprex	Visudyne			Welchol
	Mylotarg*	Zonegran			

^B New Biological * Orphan Drug

Note: the stopgap category is reserved for drugs with limited efficacy for commonly occurring conditions, ranging last year from Alzheimer's Disease to coldsores.

Prenar® is a seven-valent vaccine composed of *Streptococcus pneumoniae* capsular antigen saccharides from seven bacterial serotypes, individually conjugated to diphtheria CRM₁₉₇ protein.⁴

In clinical trials including 38,000 children, Prenar® was compared to a control vaccine. It was highly effective in preventing invasive disease caused by the seven strains of *S pneumoniae* covered by the vaccine.⁵ Its safety was confirmed. Because the Centers for Disease Control have recommended the inclusion of Prenar® in routine childhood immunizations, the incidence of pneumococcal invasive disease almost certainly will plummet in the same way *Haemophilus* invasive disease did in the past decade. *S pneumoniae* is also responsible for 30-50% of acute otitis media infections. Overall in clinical studies, Prenar® decreased the incidence of otitis media by only 10%, but was more effective in preventing frequent infections and decreasing tympanostomy tube placement.

Particularly at a time when bacterial resistance to common antibiotics has been increasing, lives will be saved and disability prevented because vaccine use will prevent the occurrence of serious infections due to *S pneumoniae*.

2. Oxcarbazepine (Trileptal®)

The effectiveness of carbamazepine as a broad-spectrum antiepileptic drug is limited by toxicities that are due in part to its active metabolite, the 10,11-epoxide. The most serious rare toxicities are aplastic anemia and agranulocytosis, but decreased platelet and white blood cell counts are common, so that close monitoring is necessary to make sure that mild abnormalities do not progress.⁶ Rarely, rashes have developed into Stevens-Johnson syndrome. Although oxcarbazepine is structurally similar, it is not metabolized via the 10,11-epoxide; fortunately it is an effective anticonvulsant and, even better, it has an improved safety profile.⁷ It is generally well-tolerated, and its most common adverse effects are headache, dizziness, nausea, fatigue and somnolence. Hyponatremia occurs rarely, but did cause about 1% of the drug discontinuations during clinical trials. Oxcarbazepine has fewer drug-drug interactions than carbamazepine. The most significant of these are interactions with phenytoin and phenobarbital that can decrease the AUC of oxcarbazepine; oxcarbazepine can decrease the AUC of ethinyl estradiol by 50% to compromise the effectiveness of oral contraceptives. Oxcarbazepine, with a pregnancy risk factor of C, is significantly safer in pregnancy than carbamazepine, which has a risk factor of D.

Carbamazepine has two labeled indications, epilepsy in adults and children, and trigeminal neuralgia, but it is used for dozens of unlabeled uses such as bipolar disorder and neuropathic pain. The availability of a safer agent should stimulate more systematic research in large patient groups who may benefit from applications that are currently unlabeled. What is not yet known is the efficacy of oxcarbazepine for the unlabeled uses.

3. Verteporfin (Visudyne®)

The rapidly progressive “wet” form of age-related macular degeneration, characterized by subfoveal choroidal neovascularization, is a leading cause of blindness in people over 50 years old.⁸ Photodynamic therapy with verteporfin is the first effective intervention to delay progression of blindness. Verteporfin is a liposomal benzoporphyrin derivative, selectively retained in rapidly growing cells, that is a potent photosensitizer. Fifteen minutes after a ten-minute IV infusion of verteporfin, a custom laser focuses light with a wavelength of 689 nm over the lesion for 83 seconds.⁹ Patients are followed every three months and retreated if angiography shows fluorescein leaks. In one multicenter study, examination after one year showed that the verteporfin-treated patients had significantly less vision loss. Although the treatment is cumbersome and does not improve vision, it greatly retards a process that, untreated, can result in functional blindness in as little as two months to three years. Verteporfin therapy already had Medicare coverage in place by the time it was approved by the FDA in April of 2000.

4. Linezolid (Zyvox®)

Vancomycin-resistant enterococci (VRE) did not emerge until 1986, 30 years after vancomycin entered clinical practice.¹⁰ In that decade, high fecal concentrations attained by use of oral vancomycin for eradication of diarrhea due to *C difficile* may have created the opportunity for selection of vancomycin-resistant species. Antibiotics like cephalosporins that are present at high levels in the gastrointestinal tract but are not active against enterococci also can lead to colonization and high concentrations of VRE in the stool. Enterococci can cause serious infections like endocarditis, meningitis and septicemia, particularly in patients who are already seriously ill. Resistance is becoming worse in hospitals. The introduction of Synercid® (quinupristin/dalfopristin) and now the first oxazolidinone, linezolid, as antibiotics of last resort, can give healthcare organizations breathing room to organize multifaceted campaigns to eradicate resistant gram-positive pathogens by improved antibiotic use patterns and infection control measures. Linezolid, available for both intravenous and oral use, starts with no pre-existing endogenous resistance mechanisms known in gram-positive bacteria, but if it is widely used without guidelines, bacterial resistance will soon become a clinical problem.¹¹

5. Diclofenac sodium gel 3% in 2.5% hyaluronic acid gel (Solaraze®)

Every year in the United States, 1.3 million people are diagnosed with actinic keratosis, a precancerous skin condition that, untreated, can progress to squamous cell carcinoma. Trials have shown that Solaraze® applied twice daily for three months clears these lesions. The mechanism of action of the

diclofenac is not known, but in the hyaluronic acid vehicle, it does penetrate the epidermis. In one open-label study, 81% of the patients had complete clearing at a median interval of 62 days.¹² In a placebo-controlled trial, 47% of 108 patients had complete clearing compared to 19% of the vehicle-treated patients after three months.¹³

6. *Abacavir sulfate/lamivudine/zidovudine (Trizivir®)*

Trizivir® is a combination of three HIV nucleoside reverse transcriptase inhibitors (NRTI) for treatment of established HIV infection. In the era of highly active antiretroviral therapy (HAART), drug treatment of HIV infection with triple-drug combinations usually including a protease inhibitor has resulted in a remarkable drop in AIDS deaths since 1997.¹⁴ At best, AIDS is still a chronic disease that requires lifelong drug treatment for those fortunate enough to afford treatment costs. With these combinations, the levels of circulating HIV in the blood drop dramatically, CD4 cell counts rise, the frequency of opportunistic infections declines, and quality of life for patients improves. On the other hand, complicated treatment regimens can be burdensome and may end in life-threatening medication non-compliance. Guidelines for treatment may be found on the HIV/AIDS Treatment Information Service website www.hivatis.org, which is jointly sponsored by the Centers for Disease Control and three other federal agencies.¹⁵ These guidelines also list drug combinations that omit either protease inhibitors or non-nucleoside reverse transcriptase inhibitors (NNRTI) to decrease adverse drug effects. One acceptable combination is a triple NRTI regime. The advantages of triple NRTI are that patients do not have the adverse effects associated with NNRTI or protease inhibitors, resistance to one NRTI does not confer cross-resistance to the whole class, and administration is simple. The dose of Trizivir® is one tablet twice daily, with or without food. The disadvantage is that long-term efficacy is unknown, because FDA approval was based on the evaluation of surrogate markers in 24-week studies. Trials to switch patients from HAART regimens with two NRTIs and a protease inhibitor to Trizivir® are in progress.¹⁶ Interim results after 24 weeks have shown continued viral suppression and improved quality of life for both groups of patients. In the Trizivir® group, both total cholesterol and triglycerides were reduced. The current AWP for a one-month supply of 60 tablets is \$1005.25.

Troubling directions in drug development policy

These therapeutic advances represent the best that pharmaceutical manufacturers can bring to improve patient care. Each drug approval represents a remarkable concentration of research acumen and large expenditures of time and money. At the same time, the marketing divisions of some of these same companies have adopted bold new strategies to improve profits without improving products. A good example is the recent

increase in the marketing of metabolites and isomers of drugs with patents near expiry.

Metabolite Marketing

Zyrtec® (cetirizine), the major active metabolite of hydroxyzine, was one of the first examples of a metabolite that was aggressively promoted and became a commercial success. Typically, a company chooses a widely prescribed drug near patent expiry and completes quick clinical studies on a newly patented isomer or a human metabolite of the same drug. The most recent example is the approval of esomeprazole (Nexium®), the S-isomer of omeprazole (Prilosec®), early this year, just in time for an impressive, large-scale marketing campaign before omeprazole loses patent protection in October (or April 2002 if the FDA approves its use in pediatric patients). The development process is virtually risk-free, brief, and free of unknowns like unexpected adverse effects. The result has absolutely no benefit for patients, but is so profitable over such a long time that one pharmaceutical company, Sepracor, does nothing but develop and market these "Improved Chemical Entities."¹⁷ Sepracor has already seen FDA approval of levalbuterol (Xopenex®) inhalation solution in 1999, and will receive cross-licensing royalties after the pending approval of desloratadine, an active metabolite of Claritin® (loratadine). Also in the wings are S-oxybutynin, S-doxazosin, two R-sibutramine metabolites (one for depression, one for ADHD) and a metabolite of R-sibutramine for sexual dysfunction. The key to success is a large sales force for professional detailing and a massive budget for direct-to-consumer advertising. For example, AstraZeneca has mounted a sales force of 3000 to promote Nexium® in the U.S. Consumers will be enticed to pay a premium for old products with new names. Even if pharmacists and physicians advise patients that these products have no advantage over the older drugs or their generic counterparts, can the truth stand against the power of big advertising?

Patent Creep

Pharmaceutical manufacturers have used ingenious strategies to prevent competitive market forces from bringing drug prices down. One such strategy has been described as "patent creep."¹⁸ Pediatric trials will extend a patent for an additional six months. Bristol-Myers Squibb has applied for and received approval for the use of Glucophage® (metformin) in children under 18 in spite of the fact that most children with diabetes are Type 1 patients on insulin therapy.¹⁹ Metformin is the only oral antidiabetic agent to have FDA approval in young patients, but the others are sure to follow, now that there is a financial stake.

Although drug patent life has already been extended by the GATT Treaty and by the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Act), drug companies have tried to prolong exclusivity by more and more

patent litigation.²⁰ The Hatch-Waxman Act grants an additional five years of patent life to innovator drugs developed after 1984.²⁰ An additional provision entitles the first company to market a generic drug for an exclusive 180-day period as the only generic on the market. The legislative intent was that as soon as a drug came off patent, the generic company could file its NDA. Companies whose major revenues come from one or two drugs nearing the end of their patent lives have placed less emphasis on expensive new research and more on relatively inexpensive litigation to prevent the old patent from ever expiring. They have filed additional patents not only on their drug, but also on the manufacturing process, its medical applications, the inert ingredients, the physical appearance of the tablet or capsule, and even the drug metabolites. In the new world of patent creep, the legal definition of “off patent” often is argued case by case.

Some legal strategies defy common sense. Last fall, Bristol-Myers Squibb attempted to create a logjam to stop the marketing of generic versions of BuSpar® (buspirone) by Mylan and Watson.²¹ On November 21, Bristol received a new patent for BuSpar® that also includes a human metabolite of buspirone. Not that Bristol intended to market the metabolite as a new drug. Their legal argument was that because the new patent also covered the drug metabolite, patent exclusivity for the parent drug should be extended. In opposition, Mylan argued that the patent could not prevent the sale of generic buspirone, and the U.S. District Court for the District of Columbia agreed. If the judge had decided in favor of Bristol, patent extensions for any drug with a metabolite could block the introduction of all generic dosage forms of that drug.

The entry of generic paroxetine to the U.S. market has been prevented by the publication of a new patent in the FDA's Orange Book.²² In 1998, after Apotex filed an application for paroxetine with the FDA, GlaxoSmithKline applied for and received a new patent for paroxetine hydrochloride hemihydrate and inserted the patent in the Orange Book. GlaxoSmithKline then began litigation in Pennsylvania claiming patent infringement, which results in an automatic 30-month stay period that precludes final FDA approval. When the stay expired, a second suit was filed. Apotex has rejoined that their anhydrous paroxetine does not violate SmithKline's patent and is seeking an injunction to have the patent removed from the Orange Book. Although the FDA has tentatively approved the generic drug, neither the FDA nor GlaxoSmithKline has yet responded to the injunction. Meanwhile, GlaxoSmithKline has caused the FDA to list eight more new patents in the Orange Book.

Direct-to-Consumer Samples

Healthcare organizations are becoming increasingly strict about controlling medication samples in ambulatory sites, and some have prohibited pharmaceutical sales representatives

from visiting physicians in their offices. Never fear! Eli Lilly and Bristol-Myers Squibb have a new strategy designated as a “broader marketing blitz” to persuade patients to remain with new versions of older drugs whose patents are expiring, in preference to more economical generic versions.²³ They are offering coupons in newspapers good for a free 30-day supply of Glucophage XR®, Glucovance® or Prozac Weekly® when used along with a valid prescription. The company that manages the coupon program freely admits that the strategy is an ingenious combination of direct-to-consumer advertising and sample distribution that frees physicians' offices from the “administrative burden of sampling.”

Occasional peccadilloes could be forgiven. Anticompetitive scheming on a large scale by so many of the established industry leaders detracts from their real accomplishments and belies their public expressions of commitment to patient health and well being. In contrast, there is no question of their commitment to their own gain and that of their stockholders.

Perspective

In the last decade, safer and more effective medications have made the attainment of therapeutic goals possible in chronic conditions such as diabetes, hypertension and dyslipidemias. Pharmacists as monitors on the healthcare team can educate and encourage patients in various practice settings to pursue these goals actively. Only in the last decade has there been clinical evidence that tight glucose control in Type 2 diabetes decreases diabetic nephropathy, neuropathy and retinopathy.²⁴ Only since 1989, when lovastatin was approved, has it been practically possible to decrease plasma cholesterol, LDL in particular, to levels that prevent heart attacks.²⁵ Invasive *H influenzae* disease now occurs in the U.S. only rarely to cause blindness and mental retardation in infants, because vaccines that work in two-month-olds are now used routinely.²⁶ Previously intractable conditions like erectile dysfunction have a pharmacologic remedy.²⁷

Yet, we complain that pharmaceutical manufacturers have lost sight of patient care in their pursuit of profits. No doubt, some of their successes will be hard to match, because they have done brilliantly. No matter how much money is poured into research and development, some problems like most cancers do not yet have effective drug treatments. Successful drug development is less like a steady stream down a pipeline than like sporadic bursts of activity that depend not only on study, intuition and effort, but also on serendipity and plain luck. The problem is that the large producers of ethical drugs are departing from ethical tactics. As health professionals and consumers, we need to make our viewpoints visible by letters to legislators and by *amicus* briefs filed by national and state pharmacy organizations. For the benefit of all, it is important for drug companies to know that the current incivility is too big a price to pay for new drugs. ■

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