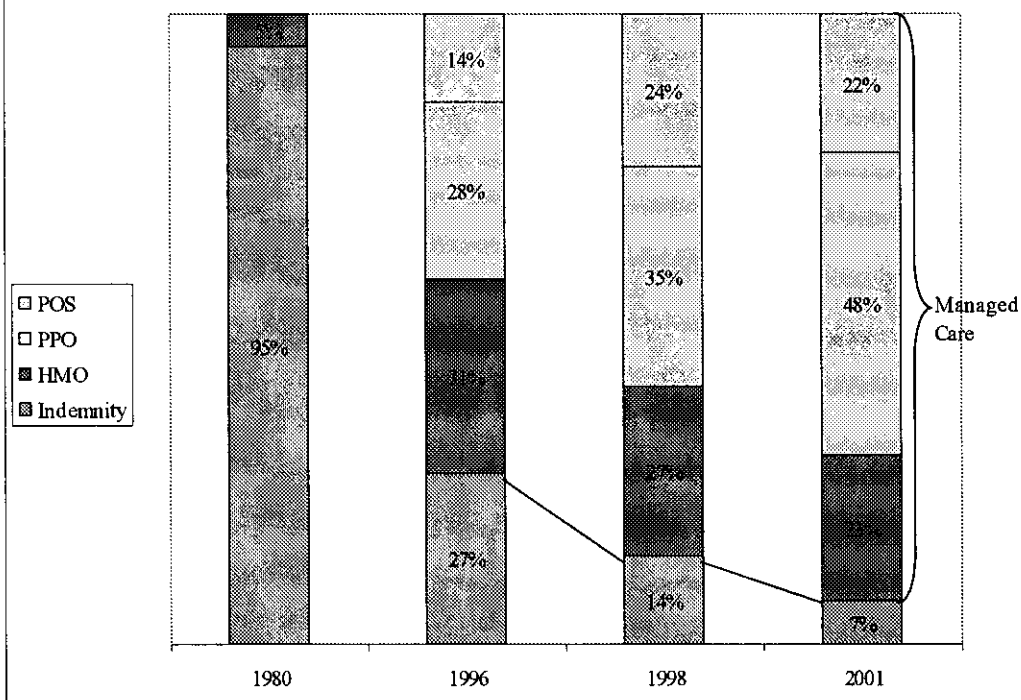
Transition to managed care brought changes to payers and purchasers as well as to providers and patients. Purchasers are typically employers that purchase health plans from payers usually known as health insurance companies, or today, as managed care organizations (MCOs). Providers include facilities, such as hospitals, skilled nursing facilities, or nursing homes, as well as personnel that provide medical services such as physicians, pharmacists, dentists, nurses and other allied professionals.

While pharmaceuticals account for only 10% of healthcare spending, they are key tools in the provider's toolkit, and the $140 billion spent in the US last year makes it a large and important industry. Pharmaceutical product development is a complex, long (10-15 years), and expensive process, with the average new drug now costing approximately $800 million to develop. Prescription, dispensing, and administration of the right drug to the right patient is a complex chain of actions involving numerous parties starting from the manufacturers, to wholesalers, pharmacy benefit managers, health plans, hospitals, physicians, pharmacists, and finally the patient.

Figure 5: Changes in Health Plan Enrollment: 1980~2001



Source: Mayer & Tanaka Managed Care Development and Innovations in the US, and their Policy Implications for Japan, Gabel et al(2001) "Job-Based Health Insurance in 2001: Inflation Hits Double digits, Managed Care

Prescription Drug Market: Manufacturers and Sellers

Manufacturers

Pharmaceutical companies can be categorized into three major groups. Major pharmaceutical companies such as Pfizer and Lilly are involved in all aspects of the product from research, development, manufacturing, to selling the drug. Whereas, smaller scale biotechnology companies and niche drug discovery companies, focus on drug discovery for certain target diseases, or specific platform technologies. The drugs discovered by these companies are often licensed out to major pharmaceutical companies for manufacturing and sales. Finally, generic drug companies manufacture drugs whose patents have expired. These companies can produce and sell the product at a lower price because they are not burdened with the research and development costs that went into the

product. Major pharmaceutical companies and generic drug companies have very different views on the pharmaceutical market.

Wholesalers

Ninety percent of prescription drug wholesaling is performed by the "Big Five" drug wholesalers: McKesson HBOC, Inc., Bergen Brunswig Drug Company, Cardinal Health, Inc., AmeriSource Corporation, and Bindle Western Drug Company. Prescription drugs are purchased in bulk from the manufacturers by these wholesalers. The drugs are stored in the wholesalers' warehouses, and then resold to retail pharmacy chains and hospitals. Since wholesalers typically purchase large quantity of drugs at a time, manufacturers benefit from reduced small volume transactions leading to reduced selling, handling and logistics costs. Purchasers on the other hand are relieved from the cumbersome process of buying only a few drugs each from several manufacturers, and the high cost of tying up capital in large amounts of inventory.

The Big Five also serve as brokers in transactions between the manufacturers and retail chains or hospitals. In these cases, the wholesaler purchases the drugs in bulk on behalf of the customer, but does not take them into inventory. Instead, they are delivered directly to the customer's warehouse. In these transactions, wholesalers generate revenue from both ends. Customers (i.e. the retail pharmacy chain or hospital) pay the wholesaler an "up-charge", a fee for the cost of distribution, and other brokerage fees. The drug manufactures pays the wholesaler a buy-side margin that consists of cash rebates and discounts for prompt and/or early payment.

The wholesaler also provide numerous other services to manufacturers, dispensers and other customers such as PBMs, contract research organizations (CROs) conducting clinical trials, IDNs and GPOs. These services include private label and control label programs whereby the wholesaler packages and labels product to meet the FDA's strict Good Manufacturing Procedures (GMP) guidelines for investigational drug trials. Wholesalers support pharmacies through promotional programs, such as providing pamphlets, signs, and

reimbursement for the retail pharmacy's advertising expenditures for specific products being promoted at that time. Generic sourcing programs enable the wholesaler to negotiate lower prices with generic manufactures on behalf of its customers, by pooling many orders together. This has contributed to more competitive generic drugs pricing. Automated third-party claims processing services facilitate real time review and adjudication of prescriptions by third party payers such as insurance companies. This allows pharmacists to perform drug utilization review (DUR) in real time and notify the patients on the spot of current formulary requirements and/or prior authorization rules. Retail zoning systems enable products to be shelved immediately by the retail pharmacy as they come delivered to the store with price labels already on each package. Some wholesalers also provide point of sale cash register systems where pharmacies are better able to manage inventory, through direct, regular transmission of inventory needs to the wholesaler, also ensuring up to date drug pricing. [6]

Under the Big Five, there are regional wholesalers, and numerous smaller sub-regional and specialty wholesalers. The regional wholesalers serve a similar client base as the Big Five, often providing some of the above value-added services regionally. In addition, there are secondary wholesalers who, instead of carrying a full product line, focus on making spot purchases of drugs occasionally on sale by manufacturers at a large discount. These drugs are then sold to other wholesalers as they are needed. [7]

Prescription Drug Market: Purchasers

Healthcare Institutions

Healthcare institutions include hospitals, clinics, nursing homes, home healthcare providers, managed care providers, government agencies, and various alternate care providers. This group in 1998 purchased approximately $25 billion in prescription drugs, 75% from wholesalers, the remaining 25% directly from manufacturers. In order to increase purchasing power for negotiating larger discounts, healthcare institutions have formed integrated delivery networks (IDNs) and group purchasing organizations (GPOs) that negotiate with manufacturers and sellers on behalf of their members. [8]

Pharmaceutical Benefits Management Companies (PBMs)

PBMs contract with major employers, insurers and MCOs to administer and provide members with prescription drug benefits at a lower cost than could be achieved by the health plan alone. The PBM typically charges the health plan a fixed per member per month fee for all drugs covered. The PBM makes a profit by acquiring and dispensing drugs needed by those members at a lower cost than the member fees. While bearing some risk, the PBM gains negotiating clout with manufacturers and wholesalers as it grows in members covered for drug benefits. In order to profitably manage the drug benefit for its members, PBMs negotiate for rebates with drug manufacturers in exchange for large volume sales, develop of pharmacy networks for its members, manage a cost-effective formulary, perform prospective and retrospective drug utilization review (DUR), and promote generic drug substitution. [9]

Retailers

Retailers include independent drug stores, retail chain pharmacies, and mail order pharmacies where patients take the prescription they receive from their physician and have it filled. America has virtually 100% "bungyo", i.e. separation of prescribing and dispensing. In the US, it is also common practice for physicians to use the telephone to order a prescription for a patient, usually after a telephone consultation and often for a refill of an existing prescription, thus saving the patient a trip to the doctor's office. Also, most prescriptions have several "refills", as decided by the doctor, where a patient can simply return to the pharmacy for an additional supply of medicine when the first batch runs out. This is particularly common for patients with chronic disease, who may take the same medicine for years. These patients may also take advantage of lower prices offered by mail order pharmacies.

Distribution and Pricing of Prescription Drugs

Regardless of their health insurance coverage status, most people purchase prescription drugs from a pharmacy. Sales for retail pharmacy outlets accounted for 90% of total outpatient prescription drug sales in 1998.

In April 2000, the Department of Health and Human Services (DHHS) conducted a study on prescription drug pricing. One segment of the study reports on the pricing of prescription drugs. Table 1 is an illustrated hypothetical example from this study showing how the brand-name drug price is set for each type of purchaser and s the amount paid by each end user. [10]

List Price

Despite its name, "average wholesale price" (AWP) is not the average of the amount paid to wholesalers by retail pharmacies. Instead it is the "list price" or suggested wholesale price promoted by the manufacturer. As shown in the table, the actual sale occurs at a discount from the AWP, which is used primarily as a benchmark. Manufacturers are free to set the price of drugs at the level they believe the market will bear, based on factors such as competition, perceived superiority versus earlier generation products, and increasingly, the pharmacoeconomic benefit of the product. Wholesale prices are not regulated. The fact that manufacturers are increasingly using pharmacoeconomics to sell their products, means that MCOs, PBMs, hospitals, and others that make purchasing decisions, especially pharmacists, must be knowledgeable in the field and able to discern good and bad assertions of benefit, based on the data presented.

In the first transaction in Table 1, the wholesaler purchases the drugs from the manufacturers at a discount from AWP, typically about 20%. From the second transaction forward, the rate of discounts and rebates begin to vary according to the purchasing power of the purchaser.[11]

Table 1: Illustrative Example of Pricing for Brand Name Prescription Drugs by Customer Type

	Cash Customers (No 3rd party payment at point of sales)	Insurers and PBMs	HMO*	Medicaid	Federal Supply Schedule
List Price (AWP)	$50				
Manufacturer's price: Manufacturer to wholesaler or other entity	$40 (AWP-20%)	$40** (AWP-20%)	$34 (AWP-33%)	$40**	$24 (AWP-52%)
Acquisition Price: Wholesaler to pharmacy	$41	$41	N/A	$41	N/A
Retail price at pharmacy: Total of amounts paid by customer and reimbursed by third party payer	$52 (AWP+4%)	$46** (AWP-13%+$2.50)		$41+$2.50	
Retail price, less typical manufacturer rebate	N/A	$30 ~$44 (5%to 35% rebate)		$30 ~$37 (15.1% to 30% rebate)	
Ultimate (net) amount paid by final purchaser and/or consumer	$52	$30 ~ $44	$34 (avg.)	$30 ~ $37 $34 (avg.)	$24

* Column refers only to HMOs that buy directly from manufacturers

** without rebate

Notes:

- Prices are based on a composite of several commonly prescribed brand-name drugs for a typical quantity of pills. For some cells in the table, the relative relationships have been calculated based on relationships reported in How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry (CBO, 1998) study and other relationships widely reported by industry sources
- Prices are used for illustrative purpose only and do not represent any type of overall average
- Prices reported in the table include both amounts paid by third-party payers and amounts paid by the consumers as cost sharing.
-

Source: Department of Health & Human Services, (2000) Report to the President: Prescription Drug Coverage, Spending, Utilization, and Prices

Cash Customers

Typically, cash customers (both those without coverage and those with less restrictive managed care health plans) pay nearly 15% more than the customer with third party drug coverage. If these cash customers have insurance, they will pay cash up front, then later submit the receipt for insurance reimbursement. Plans such as PPOs typically reimburse the member for 80% of the purchase price, but this depends on the specific health plan. The customer may be free to go to any pharmacy to get their prescription filled, or they may be directed by their health plan to a specific pharmacy, depending on the health plan.

Upon purchasing the drug at AWP, the wholesaler will sell it to the pharmacy with a slight markup, usually around 2 to 4%. The pharmacy then sells the drug to the consumer at a price that includes its cost for acquiring the drug from the wholesaler plus a retail markup. Retail markup varies by drug, but markups in the range of 20 to 25% are common.

Various pricing strategies are used since retail pharmaceutical pricing to consumers is a free market and not regulated. For example, the pharmacy may set a lower markup for maintenance medications to encourage their regular customers to return regularly, while setting a higher markup for acute medications. They may also set a deeper discount for commonly used medications as "loss leaders" in order to attract cash customers to buy other medications and non-medical products. Recently, discount warehouse stores have also opened pharmacies often selling brand name drugs cheaper than many retail pharmacies.[12]

PBMs and Insurers

PBMs can negotiate discounts and rebates from both ends of the pricing chain (i.e. from both manufacturers and pharmacies), since they represent a large number of patients and therefore wield significant purchasing power. The first type of discount is from the pharmacy. Although exact figures are not published on the level of discount offered by the retail pharmacy, it is estimated that the price paid by the PBM on a brand name drug is 13-15% off

the AWP plus a fixed dispensing fee of approximately $2.50. As shown in Table 1, the markup to the pharmacy is lower than for the cash customer, but still provides approximately a 12% markup for the pharmacy. However, there are instances where a pharmacy may be forced to accept lower payment from the PBM for a specific product, potentially even less than the pharmacy's acquisition costs. In these cases the pharmacy may have to raise its prices for cash customers to shift costs, or try to reduce its operating costs, if it wants to keep the PBM's business.

Approximately 75% of generic drugs are reimbursed by the PBM using limits know as "maximum allowable cost" (MAC). MAC is established by the PBM and is typically 50 to 60% below the AWP. The other 25% of generics are reimbursed using a similar scheme as for brand-name drug, but may have a slightly higher dispensing fee to encourage generic substitution by the pharmacies.

The second type of discount is a manufacturer's rebate to the PBM, which the PBM negotiates directly with the drug manufacturer. This is a separate transaction from the regular pricing of a drug involving the wholesaler and the pharmacy, and affects the total amount spent by the PBM. The key determining factor in the availability and the amount of the rebate is in the formulary, a list of drugs that the PBM established as the preferred products to be used by its member. If there are number of similar brand-name, or "me-too" drugs available for a given condition, the PBM may or may not include certain brands in its formulary. In addition, if a generic product is available for the condition, the PBM may encourage or require that the generic product to be used.

There is a strong incentive for a manufacturer of such a me-too brand-name drug, to give discounts to the PBM in exchange for their drug to be included in the formulary. When generic brands are also available, manufacturers offer even deeper discounts to make their own product more competitive with the generic.

There are various arrangements for the rebate to be passed on to the PBM, based on performance, e.g. the market share achieved among all prescriptions of a type for that manufacturer's product. In one such arrangement, the PBM reports the number of prescriptions for a given drug to the manufacturer. The manufacturer then pays the PBM an agreed amount for each prescription. PBMs that are contracted to an insurer or self-insured employer are typically required to pass on 70 to 90% of the rebates. [13]

HMOs and Healthcare Institutions

The direct purchasing HMO in the table receives a deeper discount than that of a PBM. This group is represented by a relatively few large HMOs, such as Kaiser Permanente, that operate their own pharmacies and internal PBMs, and buy drugs directly from the manufacturers. The majority of HMOs manage drug costs and utilization through external PBMs and do not receive these deeper discounts.[14]

Federal Facilities and Agencies

The federal government is the largest purchaser of drugs in the US, most of which is used by the Veterans Health Administration (VHA). Prices of drugs purchased by the VHA and other federal agencies are set by the Federal Supply Schedule (FSS). The VHA negotiates the FSS price with the manufacturer, and generally the prices cannot be higher than the lowest contractual price charged to any non-federal purchaser. In determining the price, the manufacturer provides the VHA with information on discount and rebates offered to other purchasers. FSS prices are generally less than half of the prices paid by other non-federal entities. [15]

Medicaid Programs

The price reimbursed to retail pharmacies by Medicaid is determined by cost limits and fixed dispensing fees. In the case of brand-name drugs where generic equivalents are not available, the cost limit is the pharmacy's cost for the specific drug. For drugs with other brand-name or generic equivalent, the limit is based on MAC. The MACs for Medicaid are published by The Centers for

Medicare & Medicaid Services every six months and set at 150% of the lowest published price for any equivalent drug, plus a dispensing fee. The Omnibus Budget Reconciliation Act of 1990 stipulates that Medicaid programs also must receive rebates from manufacturers, just like PBMs and other private purchasers. For single source drugs and multiple source drugs, the rebate is specified as the difference between the average manufacturer price (AMP), which is the average price paid by the wholesalers, and the "best" price, which is simply the lowest price offered by the manufacturer to any purchaser at any time during the year, except for federal purchasers such as the VHA. The minimum rebate is 15.1% of the AMP. For multiple source me-too drugs, the rebate is simply 11% of the AMP.[16]

Trends in Drug Prices

As mentioned earlier, the rate of increase in prescription drug costs now exceeds the rate of increase in other components of healthcare spending. Payers have criticized the pharmaceutical industry for the disproportionate increase and ultimately for the increase in healthcare expenditures. They claim that manufacturers' efforts to promote their products to consumers through billions of dollars spent on direct to-consumer (DTC) advertising further increases both the price of and spending on new drugs. The pharmaceutical industry in response states that the drug expenditure is still only about 10% of total healthcare costs. They also claim that the actual increase in drug prices is a small part of increase in drug expenditure, whereas most of the increase in drug expenditure is caused by increases in volume and switching from older less effective drugs, to newer, more effective, and commensurately more expensive, drugs. According to IMS Health, drug expenditure increased 14.7% in 2000, but less than 4% of that increase was due to price increase.[17]

Generic drug manufacturers also criticize pharmaceutical companies citing several reasons for preventing generic drugs from growing in market penetration. Generic drug utilization has ranged from 40 to 45% of all prescriptions in the last 7 years, and has not gained share during that period.[18] Generic drug manufacturers consider this rate artificially low and blame

pharmaceutical companies for erecting barriers such as brand name DTC ads, lobbying congress to enact laws discouraging generics, and manufacturer rebates for brand name products.[19]

However, while generic drug manufacturers promote the lower cost of generic drugs, the New York Times recently reported that prices of generic drugs have increased almost twice as rapidly as prices of brand-name drugs during the same period. The article reports that when the patent of a brand-name drug expires, generic drug makers charge a higher price for the first generation generics. But prices on older generic drugs are also increasing. For example, price of the generic version of the antihistamine Phenergan recently increased 900% to $309 for a thousand pills from $30 per thousand pills.[20]

Consolidation of generic manufacturers has resulted in fewer companies and less competition in the market. The five largest manufacturers now account for more than 50% of generic drug sales.[21] Despite these factors, generic drugs are still the low cost alternative to brand-name prescription drugs. On average, price of a prescription dispensed with a generic drug in 2000 was $19.93, while the average price of a prescription dispensed with a brand-name drug was $65.29. In 2000, 42% of prescriptions were dispensed with generic drugs, but consumed only 8% of the $141 billion spent on prescription drugs. On the other hand, brand-name drugs were dispensed for 58% of all prescriptions, but consumed $130 billion or 92% of the total cost of prescription drugs.[22]

Table 2: Leading Prescription Drug Sales: 2001

	Product (Manufacturer)	**Total Dollars***	**% Growth****	**% Market Share*****
1	Lipitor (Pfizer)	$5,224	25	3
2	Prilosec (AstraZeneca)	$4,611	-2	2.6
3	Zocor (Merck)	$3,680	31	2.1
4	Prevacid (TAP)	$3,553	12	2
5	Celebrex (Pharmacia)	$2,615	21	1.5
6	Epogen (Amgen)	$2,563	24	1.5
7	Procrit (Ortho Biotech)	$2,556	37	1.5
8	Zyprexa (Lilly)	$2,510	29	1.4
9	Zoloft (Pfizer)	$2,270	14	1.3
10	Paxil (Glaxo SmithKline)	$2,154	16	1.2

Source: IMS Health, Retail and Provider Perspective, 2002

*Represents prescription purchases, in millions, at pharmacy acquisition costs by retail food store chains, mass merchandisers, independent pharmacies, mail services, non-federal and federal hospitals, clinics, closed-wall HMOs, long-term care pharmacies, home healthcare and prisons/universities.

** Versus previous year

*** As a percentage of all prescription drug sales

The leading drugs by sales in the US are shown in Table 2. The number one seller, Lipitor and Zocor are lipid lowering drugs. Recent studies showing that more Americans could benefit from this kind of therapy has contributed to robust increases in sales of these competitive products. Prilosec and Prevacid are both proton pump inhibitors that reduce stomach acid in patients with gastroesophageal reflux disease (GERD) and other stomach problems caused by excess acid. Prilosec is coming off patent soon and will move to over the counter status. Celebrex is a COX-2 inhibitor, one of the new class of non steroidal anti-inflammatory drugs (NSAIDs) for the pain of arthritis. These drugs have fewer GI bleeding side-effects, though have similar effectiveness in pain relief. Epogen and Procrit are erythropoietin products made by the biopharmaceutical industry for anemia caused by a number of conditions such as cancer, kidney failure, and major surgery. Zyprexa is an anti-psychotic indicted for schizophrenia and bipolar disorder. Zoloft and Paxil are competitive selective serotonin reuptake inhibitors (SSRIs) used to treat depression and obsessive compulsive disorder. Note that most top ten drugs have me-too brand name competitors also in the top ten, illustrating the fiercely competitive nature of the market, and importance to the manufacturers of economic incentives, such as discounts and rebates, to promote their products.

Summary

Pharmaceuticals make up about 10% of the US' $1.4 trillion in national health expenditures. Health insurance in the US is provided mostly by the

private sector, though about one quarter of the population is enrolled in a government-sponsored plan like Medicare or Medicaid, and about 15% have no health insurance. Private health insurance is administered almost exclusively by MCOs, who use a variety of mechanisms to control costs and improve effectiveness, including managing the high cost of drugs through PBMs. PBMs contract with health plans to supply the prescription drug needs of members. By pooling members from many plans, PBMs gain influence, and win discounts from both supplying manufacturers and dispensing pharmacies. Wholesalers play an important role in moving drugs through the supply chain and supporting the activities of retail pharmacies. Only the largest HMOs are big enough to purchase drugs directly from manufacturers. The federal government contractually always pays the lowest price for drugs, whereas consumers that pay out of pocket pay the most. Drug prices are escalating faster than other components of healthcare expenditures, at least in part due to higher costs of drug development. It is arguable whether or not increases in volume of drug use, and switching from less effective drugs to newer more effective drugs is causing slower growth in other areas, such as hospitalization. The top ten drugs include a number of products made by competitors that compete for similar patients, illustrating the high level of competition in the market, and the importance of economic incentives as sales tools.

Section 2: The Use of Pharmacoeconomics in the US

What Is Pharmacoeconomics?

Definitions

Pharmacoeconomics has both specific and general meanings in the healthcare world. In the specific sense, it refers to specific analytic tools (e.g. cost minimization analysis, cost benefit analysis, cost-effectiveness analysis, and cost utility analysis) used to predict the total cost of introducing a specific product in a healthcare delivery setting. In the more general sense, pharmacoeconomics is an economic viewpoint applied to healthcare decision making. Pharmacoeconomic analysis is supported by a series of organizations, processes, and outputs that look beyond the efficacy and safety of a drug as reported on its FDA-approved label, to help determine what are the most effective products to use in a health care setting. Key to both specific pharmacoeconomic analyses, and the more general pharmacoeconomic viewpoint, is that one must look past the product's sales or acquisition price to the overall change in resources expended, in order to judge whether the effect of a new product or service is economically favorable in a specific setting.

New drug effectiveness may have numerous effects on healthcare utilization and ultimately costs. For example a drug for arthritis pain relief may reduce outpatient visits or even delay the need for joint replacement surgery. A drug for asthma may reduce emergency hospitalizations. At the same time, all drugs have side effects or adverse reactions in a small number of patients. These too affect healthcare utilization and costs, by necessitating an unexpected outpatient visit or even hospitalization. The pharmacoeconomic viewpoint looks at the acquisition cost, plus all changes (plus or minus) in utilization due to both efficacy as well as side effects and adverse reactions, and comes up with a value for the net effect of a new drug in a healthcare system. This should not become the only, or even the most important, way to judge whether or not to offer a new drug. But it does give an additional means by which to evaluate potential new products in addition to their clinical effectiveness and safety, especially in an era of both rising healthcare costs and increasing choices

among myriad new products. The net effect on cost may be different from setting to setting, where costs and practice patterns vary, thus each hospital and MCO needs to make their own analysis. If the economic effects are similar for multiple me-too products (i.e. products that have similar indications, effectiveness, and safety), this gives purchasers significant leverage on price during purchasing negotiations.

Parts of pharmacoeconomic analyses are applied by each constituent in the pharmaceutical value chain, from manufacture through consumption by individual patients, for different reasons and to differing extents. Manufacturers try to measure the economic benefit of a new product versus an old or competitive product, and use that information to help sell it. Physician groups and hospitals must consider the potential effect of a new product on their costs when deciding which whether to use it in surgeries that are reimbursed a fixed fee under prospective payment. Patients must individually weight the cost, safety and benefits of a new drug recommended by their doctor, something they are likely to be ill-equipped to do alone. PBMs use pharmacoeconomic analyses to help determine which drugs to reimburse under their formularies. However, even the term "cost" means a different thing to each of these constituents, depending on their viewpoints and incentives. The patient may care most about the cost of his co-payment, whereas the managed care organization may have all the data necessary to do a complete prospective analysis of the total cost to the system of introducing a new product.

The P&T Committee and Drug Monograph

The Pharmacy and Therapeutics Committee (P&T committee) is a committee typically composed of physicians, pharmacists, nurses, and administrators, whose overall objective is to maximize the quality of care involving the use of pharmaceutical products within the organization. Organizations with P&T committees include hospitals, physician groups, MCOs, PBMs, and others who have a role or influence in choosing pharmaceuticals.

P&T committees develop and maintain a formulary or list of drugs approved for use within the institution. They do this by considering all drugs suggested

for use by thorough analysis of a drug monograph, followed by discussion, and finally a decision of whether or not to includes the drug in the formulary. Often it will be a pharmacist who will prepare the drug monograph, which is a summary of key peer-reviewed data on efficacy and safety. It will likely contain data on acquisition cost, and increasingly may contain a pharmacoeconomic model projecting economic effects of the proposed new product. Formularies can be either open (i.e. physicians can use other drugs, but are encouraged to use the formulary products), or closed (i.e. only the drugs on the formulary may be used at the institution; or for an MCO or PBM, only the formulary drugs will be covered by insurance).

Other typical responsibilities of P&T committees include monitoring adverse drug reactions in the institution, establishing and monitoring prescribing, dispensing, and administration procedures, and interacting with any local institutional review boards considering clinical trials of new products within the institution. These vary by the setting and institution. It is partly through the increasing complexity of P&T committee activity, necessitating more work for the pharmacy department, that the importance of pharmacists has expanded in the US, increasing their influence.

Organizations Active in Pharmacoeconomics Policy and Promotion

Introduction

A number of organizations have an interest in standards and promotion of the use of pharmacoeconomics by P&T committees, and others responsible for drug selection. This section will review FDA regulation of pharmacoeconomic claims, the importance of pharmacoeconomic analysis to manufacturers, and the viewpoint and efforts of two pharmacists' organizations, the AMCP and ASHP. These sections are based on a combination of interviews conducted by the authors in the winter of 2003, except for the FDA, and literature review,

FDA

The Food and Drug Administration (FDA) regulates production, sales, and marketing of pharmaceutical products in the US. The FDA reviews and

approves all claims made on the product label regarding efficacy and safety, and requires minimum standards for clinical data. The FDA also has standards for how clinical trials are performed, and how outcomes are reported. Pharmacoeconomic trials and outcomes are not required by the FDA. But, many clinical trials do include outcomes that may be related to potential economic benefit of product use. For example, a product may have been shown to directly reduce utilization of specific healthcare resources such as hospitalization. A clinical outcome such as pain relief is harder to translate into economic benefit, if the manufacturer did not measure resources utilized prospectively. However, manufacturers do provide pharmacoeconomic data to P&T committees and other decision makers, and this has raised questions as to whether the FDA should regulate such analyses.

The FDA Modernization Act of 1997 does contain a section pertaining to pharmacoeconomic information: "Section 114: Health care economic information". This section was originally written as a draft guidance for the FDA by a working group of organizations under the auspices of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). The section states that health care economic information that is provided by a manufacturer to a formulary committee or similar entity "shall not be considered to be false or misleading under this paragraph if the health care information directly relates to and indication approved under section 505 or under section 351(a) of then Public Health Service Act for such drug and is based on competent and reliable scientific evidence".

But the FDA does not hold the company to the same standards for pharmacoeconomic results as they do for efficacy and safety, as the section goes on to say that, "The requirements set forth in section 505(a) or in section 351(a) of the Public Health Service Act shall not apply to health care economic information provided to such a committee or entity in accordance with this paragraph". While information related to pharmacoeconomics claims do not need to be submitted to the FDA for prior approval, the section does state that "Information that is relevant to the substantiation of the health care economic information presented pursuant to this paragraph shall be made available to

the Secretary upon request". Thus the FDA can ask manufacturers to substantiate their pharmacoeconomic claims, in case of questions.

PhRMA

The manufacturers of brand name drugs are represented by the Pharmaceutical Research and Manufacturers of America (PhRMA). With the costs of new drugs rising faster than other health care components, manufacturers are a natural target as a cause of health care inflation, particularly by payers and consumer advocates. Thus it is critical for PhRMA and its members to use pharmacoeconomic analyses to show that innovative, new pharmaceutical products contribute to overall lower healthcare costs, despite high acquisition costs (i.e. purchase prices).

Escalating drug prices are driven by the rising costs of research and development of new products. PhRMA estimates that it now costs an average of $802 million to bring one new drug to market, compared to just $231 million in 1987, and just $54 million in 1976. Members of PhRMA currently together spend more than $30 billion per year on research and development. It takes ten to fifteen years to bring a new product to market, yet only 250 of 5,000 compounds screened will enter preclinical testing. And only 5 of those 250 will enter clinical trials, with only one gaining FDA approval. [23]

That new drugs are expensive due to high R&D costs is not in debate. PhRMA uses pharmacoeconomic evidence to show that new drugs, even at high prices, can lead to lower overall healthcare costs. For example, a Medicaid program in Virginia reportedly saved $285,000 in avoided emergency room costs and urgent care visits increasing asthma drug use among its child population. Patients suffering from depression who were on antidepressant medication for at least 6 months had a reduction in their annual healthcare costs of $11,000.[24] PhRMA cites numerous similar examples.

On a higher level, PhRMA also cites work by Columbia University economist Frank Lichtenburg showing that each $1 increase in drug spending is associated with a $3.65 reduction in hospital expenditures today. Also, while

prescription drugs as a portion of total health care spending has increased from ten years ago, hospital expenditures have decreased from nearly 37% to only 33%, suggesting that new and improved drugs are substituting for more costly inpatient care.[25] It can be argued that shorter hospital stays have been enabled at least partly by innovative new drugs.

While not required by the FDA, manufacturers must increasingly build pharmacoeconomic analyses into their clinical trials, in order to generate prospective economic outcomes to show payers. PhRMA has two sitting committees related to generation of data of interest to purchasers and the FDA. The Health Outcomes and Promotion Committee, composed of a small number of manufacturer representatives that perform outcomes research, meets regularly with the FDA to discuss what is required in the way of quantity and quality of data, in order to claim specific outcomes. This knowledge may help manufacturers build outcomes into their trials that will prove more useful for showing pharmacoeconomic benefits. The Benefit/Risk Committee weighs the risks and benefits of drugs, and tries to determine why certain drugs appear to be underutilized. For example, recent studies show that as many as 32 million Americans could benefit by taking drugs known as "statins" to lower their cholesterol, yet only a fraction actually are prescribed the drugs. A pharmacoeconomic argument, backed by peer-reviewed clinical recommendations, could be used to promote statin use to MCOs, and others that bear healthcare cost risk.[26]

ASHP

The American Society of Health-System Pharmacists (ASHP) was founded in 1942 as an organization of hospital-based pharmacists. Due to the changing role of hospital pharmacies and growing role of outpatient pharmacy in patient care, the organization changed its orientation in 1995 towards supporting pharmacists in the entire health care system, though 60% of members today are still hospital-based. Virtually every hospital has a P&T committee and hospital-based committees were established before those at MCOs. The organization supports its members through publication of its journal, the American Journal of Health System Pharmacy, compilation of pharmacy