論　文

The Use of Pharmacoeconomics in the US Healthcare System

Gregg L. Mayer, Ph.D. *1
Hakugi Kiyono *1
Hiroyuki Sakamaki, M.B.A. *2

Healthcare expenditures in the United States are growing by almost 10% a year, and reached approximately $1.3 trillion in 2001. Drugs accounted for about 10% of this amount. However, the market for prescription drugs is growing at a rate of 15.7%, and has exhibited much higher growth than overall health expenditures. The expansion of managed care since the nineties has brought with it a variety of means to control health spending. Originally just in hospitals, MCOs, PBMs, and physicians groups have now also formed pharmaceutical and therapeutics (P&T) committees in order to list new drugs in and update formularies. The use of pharmacoeconomics by P&T committees in formulary control has been increasing in recent years. Pharmacoeconomic approaches to evaluating physician activities, such as the cost-effectiveness of prescribing habits, is also growing more common in hospitals and other medical care settings. Pharmacist associations and academic societies with an interest in managed care are now providing educational programs for their members and related professions, as well as guidelines to standardize the use of pharmacoeconomic analysis. Observing practical applications of pharmacoeconomics, and its results, in the US provides useful lessons for improving the use of pharmacoeconomics in the health services in Japan as well.

[key words] pharmacoeconomics, USA, drug distribution, formulary

＊1 Gregg L. Mayer & Company, Inc.
＊2 Institute for Health Economics and Policy

1. Pharmaceutical Sales and Distribution in the US

(1) Introduction

Pharmaceutical products are important tools used by physicians around the world. Nearly half of worldwide pharmaceutical sales occur in the US, with Japan a distant second at about 15%. The US healthcare market is largely a free and unregulated healthcare market, putting buyers and sellers of products, such as prescription drugs, on opposite sides of a tough negotiating table. This chapter describes the US healthcare market, health insurance, the market for prescription drugs, and how they are bought and paid for within the US' fragmented reimbursement system.

(2) US Healthcare Expenditures

Although the rate of increase has dropped below 10% in recent years, national healthcare expenditures topped $1.425 trillion in 2001, an 8.7% increase from the previous year. Approximately $1.373 trillion was spent on healthcare services and supplies. One hundred forty billion, or about ten percent, was spent on pharmaceutical products as shown in **Figure 1**. **Figure 2** shows the major categories of national healthcare expenditures. While the largest spending categories such as hospital care services ($451 billion), and physician and clinical services ($313 billion) increased by 8.3% and 8.6% compared to previous year respectively, the rate of increase in prescription drug spending ($140 billion) rose by 15.7%. The pace of prescription drug increases eased from

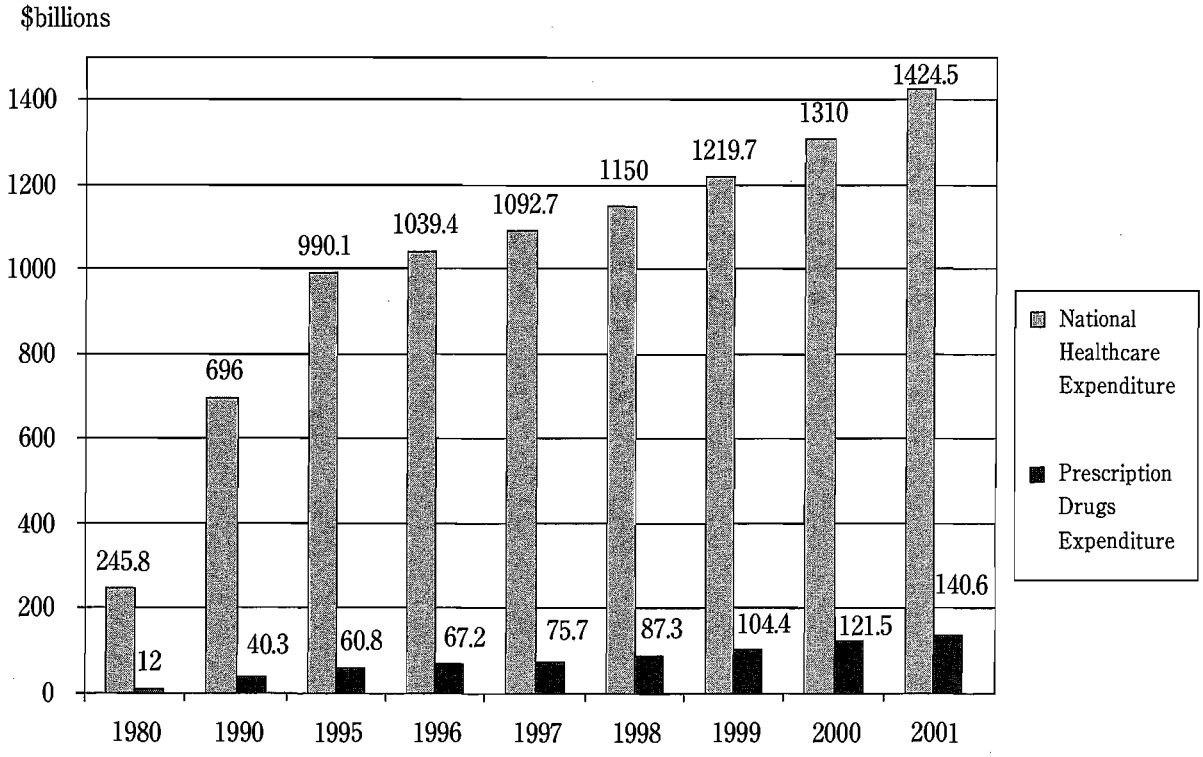

Figure 1 Growth in National Healthcare and Prescription Drug Expenditures

Source: Levit et.al., (2003) "Trends in U.S. Healthcare Spending 2001," Health Affairs January/February

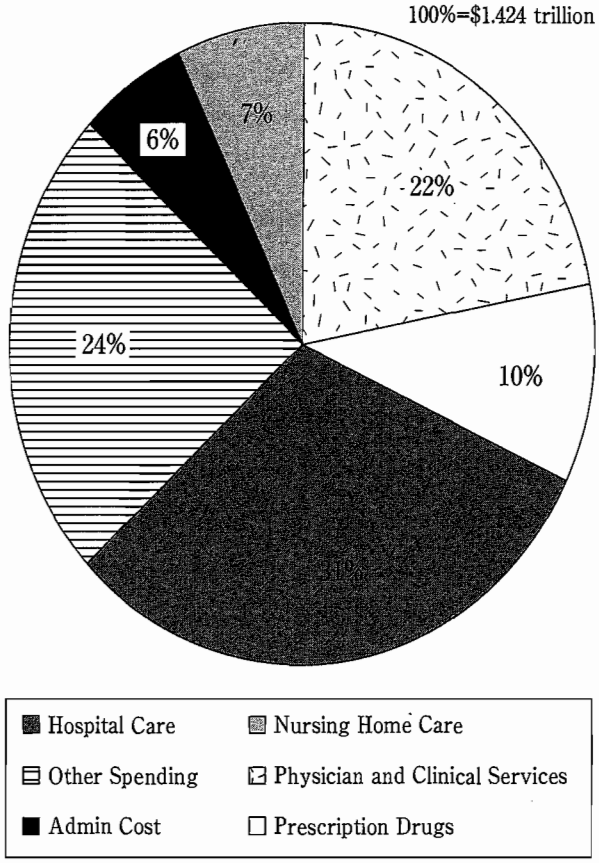

Figure 2 Components of National Health Expenditures - 2001

Source: Centers for Medicare & Medicaid Services: Health Accounts web site
Figures do not add to 100% due to rounding.
Other Spending includes dental services, other professional services, home healthcare, durable medical products, other nondurable medical products, government public health activities, research, and construction.

19.7% in 1999 and 16.4% in 2000, but was still twice as high as all other spending categories[1].

According to the Organisation for Economic Co-operation and Development (OECD), in 1998, the US had the highest per capita healthcare cost in the world, $4,165. Spending on pharmaceuticals per capita was $422, a close second to France, who spends the most per capita on drugs in the world. But the cost of pharmaceuticals as a share of total US healthcare expenditure was only 10%, one of the lowest among OECD countries. By 2001, US per capita healthcare costs had risen to $5,045[2].

(3) US Health Insurance System

The United States is unique in that it does not have a national health insurance program and 15% of the population has no insurance coverage at all. Healthcare for the uninsured is paid for directly out of pocket, or by a complex patchwork of federal, state, local government, and privately funded programs geared primarily toward the low income uninsured. Federal and state governments were the payers for about 26% of the population through Medicare, Medicaid, and other public programs. The remaining 59% of Americans are covered by private health insurance that they either receive all or in part as a benefit from their employer, or pay for themselves. Overall, public funds pay for about 46% of healthcare spending (i.e. the sum of Medicare, Medicaid, and other public spending), while private spending accounts for 54%, as shown in **Figure 3**. Within the private spending category, private health insurance paid for 35% of healthcare spending, while out of pocket spending paid for another 14%. In terms of prescription drug spending, public funds paid for about 23% of prescription drugs, while the private sector, including out of pocket spending and private health insurance, paid for 77%, as shown in **Figure 4**. Part of the reason private spending on drugs is so high, is that outpatient drugs are not currently covered by traditional Medicare[3]. In 2003, Congress passed legislation to begin to provide prescription drug coverage in 2006[4].

The US health insurance system has gone through drastic changes in the last decade. Up until the early 1980's, traditional indemnity, fee-for-service insurance coverage dominated. As the cost of healthcare started to rise rapidly, purchasers of

Clinical Management of Pharmaceuticals (CMoP). DRUG works with doctors on an ongoing basis to promote cost-effective drug use habits today, while CMoP takes a historical look at patients on off-formulary drugs for long periods of time and works with the doctor to try to understand the reasons for the off-formulary prescription.

KP's pharmacy has undertaken a number of formulary strategies to reduce the cost of drugs. For example, in the areas of antidepressants known as selective serotonin reuptake inhibitors (SSRIs), there are many products on the market, but they all have basically the same effect according to the scientific literature. Fluoxetine (Prozac) has now gone off patent and is available in generic form for a lower price then the brand name SSRIs. In turn, KP's pharmacy purchasing group has negotiated a favorable price with a generic fluoxetine manufacturer in exchange for promoting the product among their physicians. The purchasing group feels they need to be able to "deliver" between a 50-90% "market share" within KP of a single product in order to gain a favorable negotiating position with manufacturers.

The pharmacy department uses a number of methods to promote formulary products among KP physicians in order to gain necessary market share for favorable negotiations. Pharmacy offers lectures and educational literature, has a telephone consultation service where doctors can ask questions about all drug use in their patients, and has designed tools just for KP physicians. For example, pocket sized cards for doctors list the choices of drugs in a category, such as SSRIs, and note the much lower price per month to KP of prescribing fluoxetine, $44/month, versus fluvoxamine (Luvox) at $120/month or paroxetine (Paxil) at $377/month. They want the doctor to be able to see the differences in price, weigh it in with the benefits, and make up their own minds.

To track results of these efforts, DRUG and CMoP provide weekly reports of new SSRI "starts" (i.e. new patients on SSRIs) to each region, facility, and individual provider. This allows evaluation of formulary compliance at all levels, and the reasons behind non-compliance to be examined. The results of these efforts for SSRIs is that nearly 70% of new prescription starts are generic fluoxetine, accounting for only 16% of total antidepressant costs, whereas the other 30% of new starts being filled by brand name products account for the other 84% of costs. Overall, 70% of KP's prescriptions are filled by generics, which account for only 15% of total drug costs, whereas 30% are filled with brand name that account for 85% of total drug costs. In categories where generics are available, 98% of drugs dispensed are generic.

Within KP, pharmacoeconomic analysis provides additional perspectives when considering new drugs that are only marginally different than their predecessors, but sold at substantially higher prices. For example, traditional NSAIDs have come off patent, and companies have developed a new generation of NSAIDs known as COX-2 inhibitors. These products are sold primarily as being safer than traditional NSAIDs, due to reduced GI bleeding, and now account for about 1/2 the US NSAID market. The cost of the new drugs far exceeds that of the traditional NSAIDs. Using the results of a peer-reviewed study published by Stanford University researchers[33], pharmacists and their physician rheumatologist colleagues

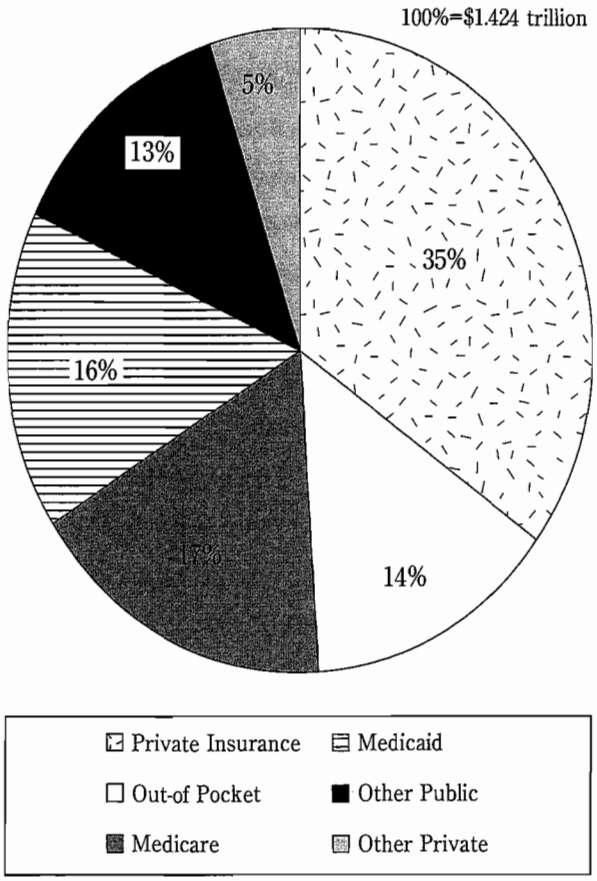

Figure 3 Sources of National Health Expenditures - 2001

Source: Centers for Medicare & Medicaid Services: Health Accounts web site

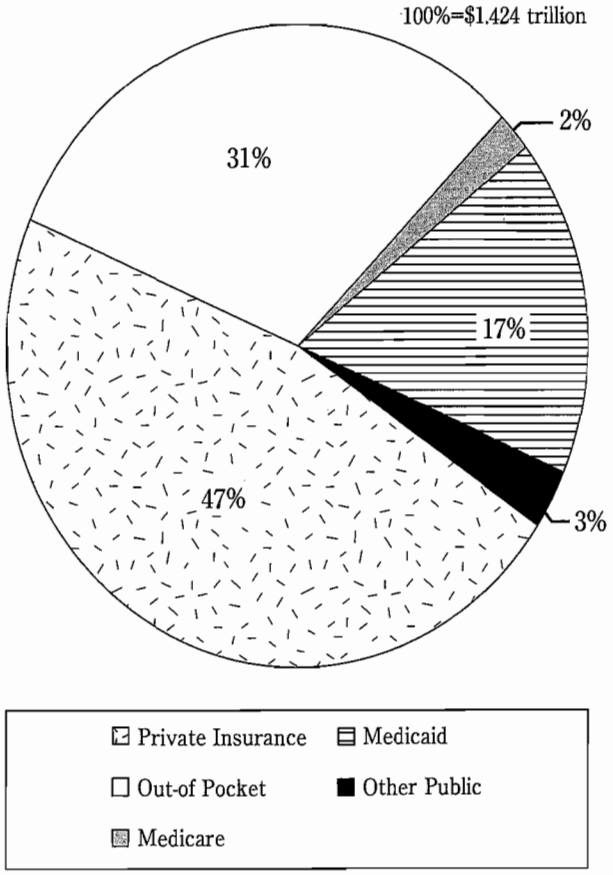

Figure 4 Sources of Payment for Drugs: 2001

Source: Levit et.al., (2001) "Trends in U.S. Healthcare Spending 2001," Health Affairs January/February

health insurance, particularly employers, began to seek ways to gain control over the growth. Health insurers responded by introducing a variety of innovative healthcare cost reduction techniques, such as utilization review, case management, and better preventive healthcare in order to reduce costs. These efforts led to the development of managed care.

The 1990s saw a rapid expansion in managed care, which can be defined as "a system of healthcare reimbursement and provision that uses financial incentives and administrative and clinical management controls to direct patients to efficient providers who are responsible for delivering healthcare in a cost-effective manner"[5]. Now over 93% of the privately insured population is covered by one form of managed care or another while only 7% percent is covered by traditional fee for service insurance, as shown in **Figure 5**. Medicare and Medicaid programs also both have substantial managed care penetration.

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.

(4) Prescription Drug Market: Manufacturers and Sellers

①Manufacturers

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

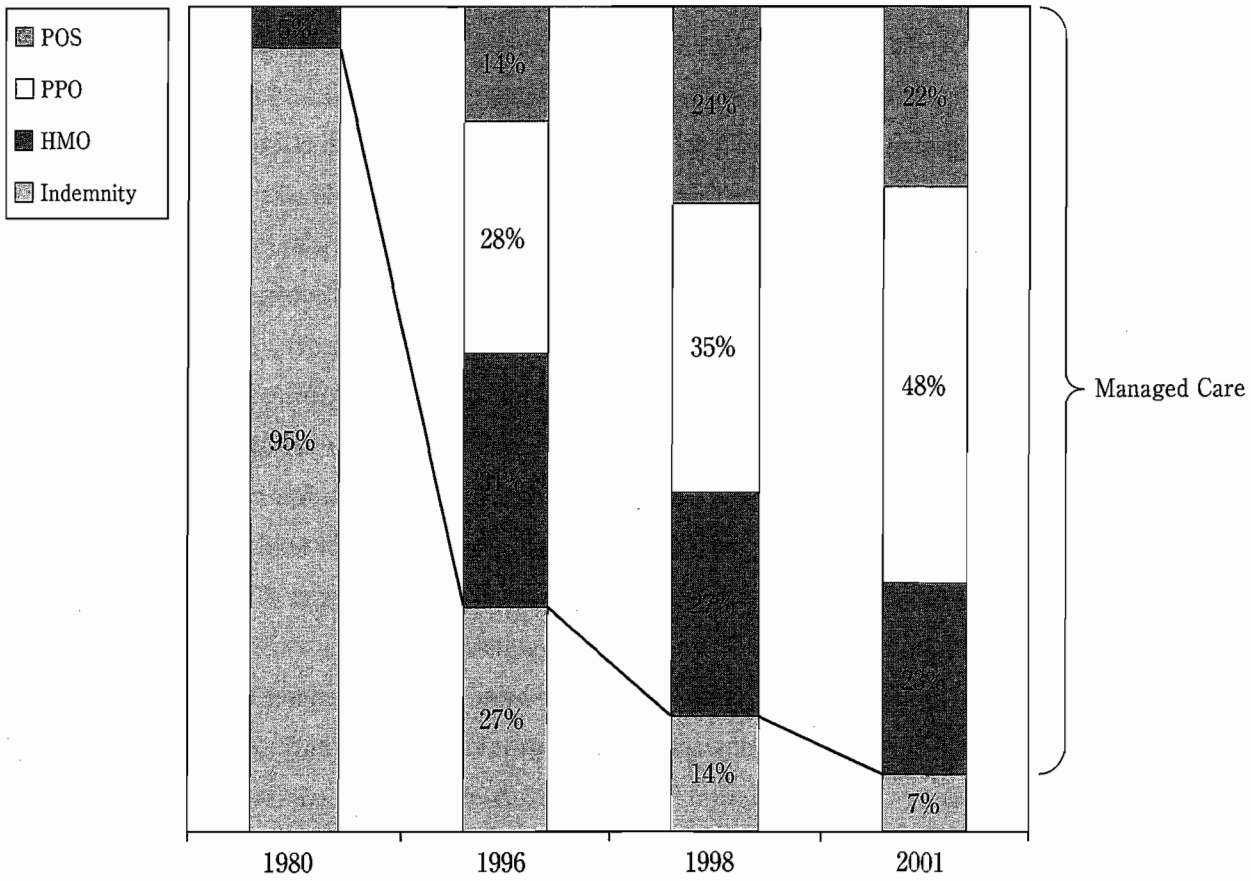

Figure 5 Changes in Health Plan Enrollment: 1980~2001

Source: Mayer & Tanaka (1997) 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 Retreats," Health Affairs, Vol.20, No.5 September/October

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.

②Wholesalers

Ninety percent of prescription drug wholesaling is performed by the "Big Three" drug wholesalers: McKesson HBOC, Inc., Company, Cardinal Health, Inc., and AmeriSource Bergen. 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 Three 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 provides numerous other services to manufacturers, dispensers and other customers such as Pharmaceutical Benefits Management Companies (PBMs), contract research organizations (CROs) conducting clinical trials, integrated delivery networks (IDNs) and group purchasing organizations (GPOs). These services include private label and control label programs whereby the wholesaler packages and labels product to meet the Food and Drug Administration (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 drug 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 Three, there are regional wholesalers, and numerous smaller sub-regional and specialty wholesalers. The regional wholesalers serve a similar client base as the Big Three, 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].

(5) Prescription Drug Market: Purchasers

①Healthcare 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].

②Pharmaceutical 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 pharmacy networks for its members, manage a cost-effective formulary, perform prospective and retrospective DUR, and promote generic drug substitution[9].

③Retailers

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.

(6) 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 the amount paid by each end user[10].

①List 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 **Table 1**, 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].

②Cash 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 Preferred Provider Organizations (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].

③Insurers and PBMs

PBMs can negotiate discounts and rebates from both ends of the pricing chain (i.e. from both

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	HMOs*	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

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 when 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 members. If there are a 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 be used.

There is a strong incentive for the manufacturer of such a me-too brand-name drug, to give discounts to the PBM in exchange for their drug being 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].

④HMOs 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].

⑤Federal 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].

⑥Medicaid 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].

(7) 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 expenditures 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].

The leading drugs by sales in the US are shown in **Table 2**. The number one seller Lipitor and number three Zocor are both 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.

(8) Summary

Pharmaceuticals make up about 10% of the US'

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

$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.

2. The Use of Pharmacoeconomics in the US

(1) What Is Pharmacoeconomics?

①Definitions

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.

(2) Organizations Active in Pharmacoeconomics Policy and Promotion

①Introduction

A number of organizations have an interest in standards and promotion of the use of pharmacoeconomics by Pharmacy and Therapeutics (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 Academy of Managed Care Pharmacy (AMCP) and American Society of Health-System Pharmacists (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.

②FDA

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 an indication approved under section 505 or under section 351(a) of the 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.

③PhRMA

The manufacturers of brand name drugs are represented by the Pharmaceutical Research and Manufacturers of America (PhRMA). With the cost 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 eventually 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 by 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].

④The 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 include 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.

⑤ASHP

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 standards of care, and sales of a number of both reference and educational books and videotapes. The ASHP describes itself as having its primary emphasis on efficacy and safety, since proper use of drugs in and of itself leads to lower health care costs[27].

Medical errors are costly and often avoidable. The ASHP emphasizes the importance of training in the safe use of medication and its standards, books and educational materials provide such support. Quality control and safety programs have lead to relatively low medication error rates in dispensing, versus prescription and drug administration. According to the ASHP, 39% of medication errors are due to mistakes in prescribing and 59% due to mistakes during administration of the drug to the patient, while only 11% occurred in the dispensing process. These results demonstrate the need for expanding the role of pharmacists into the areas of prescribing and administration support, where their expertise could help reduce errors and their associated human and economic costs.

The ASHP surveyed MCO based pharmacists in 1998 to try to understand the current use of pharmacoeconomics in MCO formulary policy formulation. The results showed a perceived quality gap in pharmacoeconomic data used by drug companies to market their products. While 58% of those pharmacists surveyed said drug companies use pharmacoeconomic data to sell to MCOs, only 33% said that the information was of high quality. Furthermore, 94% said they would like to see more scientifically rigorous pharmacoeconomic studies from drug makers, and 71% felt their MCO was in a position to put pressure on manufacturers to conduct more rigorous studies. Ninety percent felt that the FDA should apply the same rigor in assessing a manufacturer's pharmacoeconomic claims as it does in assessing clinical claims, and 96% felt the FDA should apply the FTC's "competent and reliable" evidence standard in assessing pharmacoeconomic claims[28].

Currently about 45% of pharmacists surveyed said their MCO uses the pharmacoeconomic data provided by manufacturers, in making formulary decisions. While 76% of pharmacists said they were well equipped to critically analyze pharmacoeconomic data supplied by manufacturers, only 38% felt that the physician members of their MCO P&T committee were similarly well-equipped. Fifty percent of those surveyed said that at least one pharmacist in their MCO was well trained to conduct pharmacoeconomic studies, and 51% said their MCOs routinely used their own pharmacoeconomic analyses when making formulary decisions. The results of this survey suggested that in 1998, there was much work to be done in improving the quality of data supplied by manufacturers for pharmacoeconomic analysis, as well as the capabilities of MCO-based and other P&T committees to both critically analyze and perform

their own analyses. Pharmacists need to play an important role on such committees for their work to be effective[29].

⑥AMCP

The Academy of Managed Care Pharmacy (AMCP) is a more recently established pharmacist organization that promotes the use of managed health care concepts by the profession. The organization publishes a journal, offers continuing medical education (CME) for pharmacists, and performs research. Without knowledge and training in managed care concepts such as pharmacoeconomics, pharmacists are limited to the traditional role of dispensing of drugs from either hospital-based or retail pharmacies. However, with adequate training, pharmacists can work side by side with physicians, and hospital and health plan executives, in such roles as managing the medication of the chronically ill through the practice of clinical pharmacy, planning and implementing patient safety programs such as drug utilization review, promoting effective patient education, developing hospital, MCO, and PBM formularies and designing health insurance benefits programs[30].

The AMCP has also recently become concerned about the quality of pharmacoeconomics analysis going into formulary development by the P&T committees at MCOs and hospitals in the US. Both the inputs and methodology vary greatly among such organizations, and poorly performed analyses can lead to unsound formulary development. In 1999, the AMCP together with the ASHP, the National Committee for Quality Assurance (NCQA), the American Medical Association (AMA), and the Department of Veterans Affairs, joined a coalition of 50 organizations in issuing the "Principles of a Sound Drug Formulary". These are the guiding principles from this document, published in 2000:

- "Formulary system decisions are based on scientific and economic considerations that achieve appropriate, safe, and cost effective drug therapy
- The formulary system encompasses drug selection, drug utilization review, and other tools to foster best practices in prescribing, dispensing, administration, and monitoring outcomes
- The P&T Committee or equivalent body, comprised of actively practicing physicians, pharmacists, and other health care professionals, is the mechanism for administering the formulary system, which includes developing and maintaining the formulary and establishing and implementing policies on the use of drug products
- Physicians and other health care professionals provide oversight of the formulary system
- The formulary system must have its own policies, or adhere to other organizational policies, that address conflicts of interest and disclosure by P&T committee members
- The formulary system should include educational programs for payers, practitioners, and patients concerning their roles and responsibilities
- The formulary system should include a well-defined process for the physician or other prescriber to use a non-formulary drug when medically indicated"

With regard to economic considerations, the Principles specifically state that formulary decisions should be based on "cost factors only after the safety, efficacy, and therapeutic need have been established". It goes on to state that evaluating drug cost should be based on the impact on total health care cost. Finally it mentions that financial incentives should only be used to promote cost management as a part of the delivery of quality medical care, and should not interfere with the delivery of medically necessary care. The Coalition has defined an important role for pharmacoeconomic analysis, but only to the extent that it is used as a part of delivering high quality health care, and never to defend the delivery of second rate care. It also promotes open disclosure of potential conflicts of interest among P&T committee members, since many participate in clinical trials and continuing medical education sponsored by the same manufacturers. These activities are normal, but how the committee ensures that manufacturer support does not influence formulary decisions is key to the credibility of the process.

The AMCP has gone one step further and issued a Format for Formulary Submissions, beginning with Version 1.0 in 2000 followed by Version 2.0 in 2002. This serves as a guide for P&T committees to request information from pharmaceutical manufacturers to be used in preparation of a drug monograph. It describes the sections of a complete formulary submission dossier as containing the following sections:

1. "Disease and Product Information
2. Supporting Clinical and Economic Information
3. Cost-Effectiveness and Budget Impact Model Report
4. Product Value and Overall Cost
5. Supporting Information: Reprints, Bibliography, Checklist, Electronic Media, and Appendices"

It goes on to describe the recommended steps for this dossier submission, whose key points include:

1. "As manufacturers should keep managed care organizations aware of the status of their pipelines, approximately 6 months before anticipated new product launch, the pharmacy staff will issue a request for information to the manufacturer, with above-specified content.
2. The manufacturer and pharmacy staff will hold a pre-submission meeting to discuss the submission of the requested data, establish a deadline, and resolve any issues around data secrecy, economic model assumptions, etc.
3. The manufacturer should provide the report in both paper and electronic forms to the pharmacy staff at least 2 months prior to the product review
4. The pharmacy staff reviews and requests any needed clarification of the data before preparing a product monograph for P&T committee review
5. Clinical pharmacists prepare the monograph, including all data, and arguments both pro and con inclusion of the product in the formulary
6. Upon reaching a recommendation, the P&T committee will inform the manufacturer of its decision, the rationale for a denial or restriction, and the standard appeals process."

It is unknown just how many P&T committees

use the AMCP guidelines, dossier request format, and schedule, but to date, more than 300 pharmacists have been trained in its use. The AMCP hopes that these guidelines and training will move the formulary process away from discussions of single product acquisition price and rebates, and on to the effect of the formulary on the health and well-being of the population. Transparencies in all these procedures can also help erase suspicion about the inappropriate use of financial incentives in the multibillion dollar pharmaceutical and managed care industries. Clearly this AMCP initiative is also doing much to raise the influence of pharmacists in hospitals and MCOs[31].

(3) Pharmacoeconomics in Use

①Introduction

MCOs, hospitals and physician groups all use P&T committees to determine and manage drug formularies. Kaiser Permanente and the Veterans Health Administration are two particularly innovative integrated healthcare delivery systems that have focused on the opportunity to actively manage drug selection within their systems, and employ pharmacoeconomic analysis. Each has promoted the role of pharmacist from merely dispensing drugs to patients, to a more equal partner in the analysis, selection, and proper administration of drugs to the benefit of both physician and patient. In addition, pharmacists in both organizations are involved in innovative programs to more effectively use drugs.

②Kaiser Permanente

Kaiser Permanente (KP) is a large, group practice health maintenance organization (HMO), based in Oakland, California. The non-profit health plan has approximately 8.4 million members, mostly in California. The medical group, serving KP's members exclusively, has more than 11,000 physicians of all specialties. The HMO is fully integrated, meaning it operates its own hospitals, outpatient clinics, pharmacies, laboratories, and all other ancillary services. KP owns 29 hospitals and 423 outpatient clinics exclusively for the use of its members. Members (or their employers) pay an annual premium, plus modest co-payments at the time of service, for all their healthcare needs for the year, including prescription drugs. The medical group, hospitals, pharmacy, etc. must perform all their activities within this pre-determined budget of total premium revenue. This financial arrangement aligns the incentives of the hospital, physician, and member, to keep the patient healthy and out of the hospital[32].

As discussed above, pharmaceutical products are a significant and growing portion of health care spending in the US, and KP is no exception. KP spends approximately $2.5 billion per year on prescription drugs. But KP has unique advantages compared to the normally fragmented system of health care financing and delivery in the US. As a large purchaser, KP can negotiate directly with manufacturers. As a closed system of health plan, doctors, hospitals, and pharmacists, KP has the ability to more proactively use the results of pharmacoeconomic analysis to manage the cost-effectiveness of the drugs dispensed to members. KP can expose all of its physicians to information on an ongoing basis about which drugs are preferred and why, and also given feedback on their use of preferred versus non-preferred drugs.

They can also control access to KP physicians by drug company sales reps. Pharmacists play an integral role in pharmacoeconomic analysis, selection of cost-effective drugs for the formulary, and development of methods to assure formulary compliance.

KP has a number of organizations supporting cost-effective use of drugs. Two internal research groups are Drug Information Services (DIS) and Pharmacy Outcomes Research Group (PORG). PORG has a staff of 5, including 3 pharmacists, who undertake prospective and retrospective studies in the area of cost-effectiveness, variation in drug utilization, program evaluation of pharmacy clinics, and study of both clinical outcomes and associated use of health care resources. PORG is essentially an in-house pharmacy think tank.

DIS has a staff of 37, including 20 pharmacists, and is a part of the Pharmacy Strategy and Operations Group in KP's California Division. Nine of the pharmacists are specialists in specific therapeutic areas, such as cardiovascular, anesthesiology/pain, etc. Since the pharmacists specialize, they develop working relationships with specialist physicians in the same areas. DIS has responsibility for administering the formulary process. In addition, they prepare a forecast of drugs likely to be approved next year, for what indications, and at what cost to KP. They also provide a number of pharmacy information services to KP members and physicians.

KP has an open formulary which means that while use of formulary drugs is expected and encouraged, doctors are still free to prescribe any drug, under an exception rule. As a principle, all drugs submitted for the KP formulary by physicians are considered for inclusion. The P&T committee meets 4 times per year. In the end, a consensus is achieved, and the whole committee gets behind the decision of whether or not to include a specific drug. The process is dynamic, in that any time new information becomes available, a decision can be reconsidered at the next meeting. In the interim, if new drugs are approved by the FDA they can be used immediately by KP physicians under the exception rule. Similarly, if significant side-effects are found in the interim between meetings drugs could be removed from the formulary immediately.

The formulary process begins by preparation of a monograph by DIS. They gather all information available about a product, from peer-reviewed articles, to advertising pamphlets. They request an AMCP format dossier from the manufacturer, including any pharmacoeconomic models on a CD-ROM, so they can be manipulated, including adjusting cost assumptions to match KP's actual costs. Apparently large companies have implemented the AMCP format, while many smaller companies have not. DIS will consider the economic effects of both the effectiveness and safety (e.g. the cost of expected side-effects) when modeling the economic impact of a drug. They will use the manufacturer's model, if available, and model how the drug changes the use of all associated resources.

KP's Pharmacy Division operates the pharmacies and purchases pharmaceutical products in line with P&T committee policies. Within the Pharmacy Division, the Drug Use Department contains two groups that work with the P&T committees specifically to promote more cost-effective drug use, the Drug Utilization Group (DRUG) and

developed a gastrointestinal bleed risk scorecard, that easily fits in a physician's pocket. The card has an easy to use flow chart that determines which patients really need the additional GI protection from the COX-2 inhibitors. Based on the assessed risk, it recommends categories of drugs, and lists the name and price of each drug available. This allows the doctor to easily assess the patients true need for a COX-2 inhibitor at $30-120 per month, versus a traditional NSAID at $2-5 per month[34]. Recently published results showed that due to these efforts, use of COX-2 inhibitors in lower-risk patients was reduced 66% in KP Northern California patients. Total COX-2 inhibitor prescriptions were only 4% among KP members, versus 45% for patients outside KP[35].

③VHA

The Veterans Health Administration (VHA) is an integrated healthcare system serving the needs of US veterans. The VHA has a budget of more than $22 billion, employs 180,000 healthcare professionals, and operates 163 hospitals, 800 clinics, 135 nursing homes, and a variety of other facilities for its beneficiaries. As the federal government is the largest purchaser of drugs in the US, the VHA is actively involved in efforts to promote cost-effective drug use[36].

The VHA National Drug Formulary lists drugs that must be available at all VHA medical centers, and contains about 80% of drugs dispensed by the VHA. At the national level, the VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel consists of physicians and pharmacists that maintain the formulary and VHA pharmacy policies. This national formulary, along with all drug monographs, VHA drug pricing, and a variety of other information about VHA drug policy is available on-line at www.vapbm.org. In addition, each of the 21 regions has its own P&T committee and formulary, based primarily on the national formulary. Each regional committee can add drugs to its formulary with permission of the national formulary committee. Finally, there are also P&T committees at each VHA medical center that review local drug policy and use.

A brief look at some of the VHA National PBM Drug Monographs available on the Internet shows that acquisition price of the new drug is listed in comparison to existing drugs, and other costs that may change as a result of introduction are described in the conclusions and recommendations. Pharmacoeconomic benefit is analyzed when considering drugs for the national formulary, and compared with all other potential outcomes. In the San Francisco region, the P&T committee has also begun to analyze older, expensive drugs, such as proton pump inhibitors and gabapentin, to look at whether they are used effectively and determine guidelines for more cost-effective treatment of patients with cheaper drugs when possible, similar to efforts at KP. The VHA also provides its own tools to promote physician use of the formulary and cost-effective prescribing, such as physician pocket guides.

VHA pharmacies serve both in- and outpatient populations, with about 90% of prescriptions filled for outpatients. The pharmacies have introduced automation, and for example, the San Francisco VHA Medical center fills approximately 2,500 prescriptions per day, 1,500 of which are mailed to patients. The pharmacy department employs 55

persons, half of whom are pharmacists and the other half technicians. The efficiency achieved through automation has allowed the pharmacists to concentrate more on the work of clinical pharmacy, spending time consulting with patients and physicians about drug choice, dose adjustment, and patient compliance[37].

A recent example of a project spearheaded by VHA clinical pharmacists expanding their role and influence in the VHA was in the area of drug misuse and potential benefit of clinical pharmacy intervention. The VHA estimates that misuse of drugs costs the US healthcare system more than $70 billion per year in avoidable medical costs. This study evaluated the recommendations and interventions of clinical pharmacists on patient outcomes, healthcare cost, patient harm avoidance, and physician acceptance of the recommendations, in out, inpatient, and skilled nursing facility settings. Examples of typical interventions were in cases where upon pharmacist review of a physician prescription, the pharmacist recommended a dosage change to optimize therapy, or because of potential drug interactions, recommended changing the drug to minimize patient toxicity.

Overall, 92% of 600 such interventions recorded during the study period were accepted by the prescribing physician, leading to improved clinical outcomes in over 30% of cases, and no change in outcome in 40%. The interventions saved $1,000, $325, and $745, in inpatient, outpatient, and skilled nursing facility settings, respectively, for an average savings of $700 per clinical pharmacist intervention. Even when adding in the cost of the clinical pharmacist, the study showed overall reduced costs of errors of 20%. The computer system used to track the interventions and outcomes is now in place nationwide in the VHA[38].

④Summary: Pharmacoeconomics in the USA

Pharmacoeconomics refers to both specific economic analyses, and the viewpoint of including costs when considering the purchase of new medical products and services in addition to effectiveness and safety. However, each constituent of the healthcare world uses what is loosely referred to as pharmacoeconomics differently, depending on what their goals are. The result is often a confusing mixture of anecdotes and analyses, that may be of little value to many stakeholders. P&T committees at hospitals and MCOs must choose new pharmaceutical products for their patients using data on effectiveness, safety, and increasingly, pharmacoeconomics. The drug monograph is a dossier containing data that the P&T committee uses to help make formulary decisions regarding new drugs. A number of organizations have a stake in the growth of pharmacoeconomics. The FDA does not require pharmacoeconomic studies for new drug approval, but does regulate the use of outcomes data critical to quality analyses. PhRMA, as a representative of large drug manufacturers, broadly promotes the use of pharmacoeconomics in part to justify the high price of new pharmaceutical products. The ASHP is the oldest professional pharmacy organization, representing primarily hospital-based pharmacists. A recent study of their members reported that while 58% of pharmacists said that pharmaceutical companies use pharmacoeconomic data to sell to their MCOs, 94% said they would like to see more scientifically rigorous studies from makers. The AMCP promotes managed care

concepts, including pharmacoeconomics, among its pharmacist members, many of whom sit on P&T committees. The AMCP recently published a suggested format for more complete and rigorous dossiers to be submitted by manufacturers to such committees, including more rigorous pharmacoeconomic models. Within this environment, two integrated healthcare delivery organizations, KP and the VHA, are actively promoting efficient formulary policies, including the use of pharmacoeconomic analyses. Increased availability of both good and bad pharmacoeconomic analyses requires pharmacists trained in the art to help providers, PBMs and MCOs use such analyses to the maximum benefit of the patient population, and not just to any one specific stakeholder.

(4) Implications for Japan

Japan is facing a future of increasing healthcare costs, due primarily to its aging society. In order to maintain its low proportion of GDP spent on healthcare, Japan will have to introduce pharmacoeconomic analysis as one new pillar of new product evaluation from the viewpoint of efficient healthcare resources utilization.

A comparison of drug utilization under the Japanese and U.S. health care systems reveals use in Japan to be characterized by a national formulary, the determination by central government of fixed prices and national standardization of insurance reimbursement, the still incomplete separation of medical practice and drug dispensation (*bungyo*), and an immature generic drug market.

In the U.S., virtually no use is currently made of pharmacoeconomics in government regulation, unlike in Australia and Canada. However, there is strong interest in pharmacoeconomics among medical professionals and facilities, including government-run institutions such as the VHA, due to the high level of interest in managed care and the efficiency of medical care provided by medical institutions.

Bearing in mind the differences between the markets in the two countries, we need to consider the key points for successfully introducing pharmacoeconomics in Japan. Let us consider first the potential for use of pharmacoeconomics in the inclusion of drugs in the insurance formulary and determination of officially fixed prices. In the U.S., the FDA does not use pharmacoeconomics in its approval of new drugs, and there is less outpatient drug reimbursement under public insurance such as Medicare, thus there is not much to learn in this situation.

However, considering the impact of private insurers and managed care in particular on the cost of health expenditures in the U.S., the use of pharmacoeconomics in determining the inclusion of drugs in Japan's national formulary could help to control health expenditures in Japan. As it is difficult to conceive of only some new drugs approved by the government becoming recommended for such a national formulary, pharmacoeconomics' role would most likely be as a guide for determining prices at the national level.

For insurers, as payers, to use pharmacoeconomics requires that each insurer should have its own formulary containing its own recommended drugs. This would mean the intervention of insurers in the prescription of drugs

by physicians, which would give Japanese insurers greater powers than at present, as with managed care in the U.S.

In the healthcare service market (including drugs), the market mechanism is not considered to function well, due especially to the asymmetry of information between non-physicians and physicians. Those involved in the supply and demand for healthcare services in the U.S., however, use pharmacoeconomics as a source of data complementing market mechanisms in order to engage in more efficient decision-making.

In Japan, too, the optimum types and uses of drugs need to be selected by medical institutions, as the patients' proxies, using appropriate information incorporating data on cost performance. In this case, the process of *bungyo* must be completed on the provider side such that there are no remaining incentives for physicians to dispense one drug over another, or any drug at all, to their outpatients. The new prospective payment system will also need to be spread to all hospitals, such that drugs used for inpatient care become viewed as costs, not sources of income. With these changes, hospital P&T committees will have a reason to discuss pharmacoeconomics when choosing new drugs. This will create a larger role for pharmacists on these committees. The pharmacy profession will have to introduce new educational programs for its members and promote new standards for data analysis and evaluation.

Insurance benefits in Japan are paid on a fee-for-service basis, giving individual medical institutions little incentive to reduce medical expenses. Controlling health expenditures overall therefore requires that economic evaluations be made of drugs at the level of payers (insurers) and the central government. However, the increasing use of per diem insurance benefits (e.g. with the recent introduction of the Diagnosis Procedure Combination (DPC) system) will increase the importance of pharmacoeconomic studies in medical institutions in Japan[39].

Finally, when the reimbursement changes above take place such that saving money in healthcare becomes important to their customers, manufacturers will have to provide more pharmacoeconomic data to sell their products ahead of the competition, and to justify the high cost of new products. This change will emphasize the need for the pharmacist profession to become a leader in pharmacoeconomics, and guide their institutions away from making decisions based on poor or inadequate analyses, to solid evidence-based ones.

References

1) Levit et.al., (2001) "Trends in U.S. Healthcare Spending 2001," *Health Affairs* January/February

2) OECD (2001) "*Health at a Glance*"

3) http://www.cms.hhs.gov/statistics/nhe/historical/chart.asp

4) Centers for Medicare and Medicaid Services : Medicare website. The Facts about Upcoming New Benefits in Medicare. Downloaded from http://www.medicare.gov/MedicareReform/

5) Mayer, Gregg L. and Tanaka, Shigeru, "Managed Care Development and Innovation in the US, and Their Policy Implications for Japan", *Journal of Health Care and Society*

7(1): 109-127, May, 1997

6) Department of Health and Human Services. Food and Drug Administration 2001. The Prescription Drug Marketing Act Report to Congress.Downloaded from http://www.fda.gov /oc/psma/report2001/

7) ibid

8) ibid

9) ibid

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

11) ibid

12) ibid

13) ibid

14) ibid

15) ibid

16) ibid

17) IMS Health, *Pharmaceutical Pricing Update*, 2001

18) Generic Pharmaceutical Association web site: http://www.gphaonline.org

19) ibid

20) Fruedenheim, Milt, "As Drugs Patents End, Cost for Generics Surge," *The New York Times*, 27 December 2002

21) ibid

22) Generic Pharmaceutical Association web site: http://www.gphaonline.org

23) Interview with PhRMA, 2/14/03

24) In "*The Value of Medicines*", published by PhRMA 2003

25) ibid

26) Interview with PhRMA, 2/14/03

27) Interview with ASHP, 2/13/03

28) ASHP Pharmacoeconomic Survey, August, 1998

29) ibid

30) Interview with AMCP 2/13/03

31) ibid

32) Interview with Kaiser Permanente 2/10/03

33) Singh, et. al. "GI Score: A Simple Self-assessment Instrument to Quantify the Risk of Serious NSAID-Related GI Complications" Arthritis Rheum 1998 Sep; 41(9 suppl): S75

34) Interview with Kaiser Permanente 2/10/03

35) Hyatt, et. al., "Improving Appropriate Prescription Drug Use to Best Practice: Supporting Evidence-Based drug Use", *The Permanente Journal* 7(2), Spring 2003

36) Interview with VHA Medical Center Pharmacy Staff, San Francisco

37) ibid

38) Boro, et. al., 2002, "Clinical and Economic Outcomes of Pharmacists recommendations in a Veterans Affairs Medical Center" *Am J Health Syst Pharm* 1; 59(21): 2070-7

39) ShinyaMatsuda: Influences on the utilization and distribution of drugs and medical devices by DPC. ShinyaMatsuda ed. Medical care in 21th Century and DPC. p57-66 Jiho 2003, Tokyo (in Japanese)

Address correspondence to:

Gregg L. Mayer
Hakugi Kiyono
Gregg L. Mayer & Company, Inc.
7019 Stockton Avenue, El Cerrito, California 94530
USA
TEL +1-510-559-3200
FAX +1-510-559-4044
E-mail : gregg@glmco.com

Hiroyuki, Sakamaki
Institute for Health Economics and Policy
1-5-7, Nagata-cho, Chiyodaku, Tokyo, 100-0014,
Japan
TEL +81-3-3506-8529
FAX +81-3-3506-8528
E-mail : sakamaki@ihep.jp

Glossary

AMA	American Medical Association
AMP	average manufacturer price
AMCP	Academy of Managed Care Pharmacy
ASHP	American Society of Health-System Pharmacists
AWP	average wholesale price
CME	continuing medical education
CMoP	Clinical Management of Pharmaceuticals
COX-2	cyclooxygenase-2
CRO	contract research organizations
DHHS	Department of Health and Human Services
DIS	Drug Information Services
DPC	Diagnosis Procedure Combination
DRUG	Drug Utilization Group
DTC	direct to-consumer
DUR	drug utilization review
FDA	Food and Drug Administration
FSS	Federal Supply Schedule
GDP	Gross Domestic Product
GERD	gastroesophageal reflux disease
GMP	Good Manufacturing Practice
GPO	group purchasing organization
HMO	health maintenance organization
IDN	integrated delivery network
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KP	Kaiser Permanente
MAC	maximum allowable cost
MCO	managed care organization
NCQA	National Committee for Quality Assurance
NSAID	non steroidal anti-inflammatory drug
OECD	Organisation for Economic Co-operation and Development
P&T Committee	Pharmacy and Therapeutics Committee
PBM	Pharmaceutical Benefits Management
PhRMA	Pharmaceutical Research and Manufacturers of America
PORG	Pharmacy Outcomes Research Group
PPO	Preferred Provider Organization
R&D	research and development
SSRI	selective serotonin reuptake inhibitor
VHA	Veterans Health Administration

米国ヘルスケアシステムにおける薬剤経済学の利用状況

Gregg L. Mayer*1
Hakugi Kiyono*1
坂巻弘之*2

米国の医療費は、毎年10%近い伸びを示しており、2001年には約1兆3000億ドルが支出された。そのうちの薬剤費の割合は約10%であるが、処方薬の市場の伸びは15.7%であり、ここ数年、全体の医療費の伸びに比べ大きな数値を示している。一方、1990年代以降のマネジドケアの拡大は、さまざまな手段で医療費コントロールを行っている。マネジドケアにとどまらず、PBM、病院、医師グループは、フォーミュラリーへの新薬の収載、更新のためにP&T委員会を組織しており、近年、フォーミュラリーコントロールに薬剤経済学の利用が進んでいる。また、病院など医療現場では、薬剤師が自らの業務を経済的に評価するなどの形でも薬剤経済学の考え方が浸透しつつあり、マネジドケアに関連する学会や薬剤師団体では、薬剤経済学データの利用の標準化のためにガイドラインや関係者への教育プログラムを提供している。米国における薬剤経済学の利用方法は、日本においても医療の現場で薬剤経済学を用いる際の参考になると考えられる。

キーワード：薬剤経済学、米国、医薬品流通、フォーミュラリー

＊1　Gregg L. Mayer & Company, Inc.
＊2　医療経済研究機構