PRESCRIPTION DRUG PRICES:
FINDINGS FROM INTERNATIONAL COMPARISONS AND A DOMESTIC STORY

A REPORT

OF THE

MAJORITY STAFF OF THE SPECIAL COMMITTEE ON AGING
UNITED STATES SENATE

July 21, 2011

As Chairman of the Special Committee on Aging, Senator Kohl authorized information requests on prescription drug pricing as part of two separate inquiries. The first inquiry sought information from pharmaceutical companies regarding the disparity in American pricing when compared to other developed countries. The second inquiry, with Representatives Waxman, Pallone and DeGette, senior members of the House Energy and Commerce Committee, sought information on how two pharmaceutical companies set prices for two newly Food and Drug Administration (FDA) approved drugs. This report summarizes the Committee's findings from the information collected from these inquiries.

PART I: Inquiry on Drug Prices: Comparing U.S. to Foreign Market Drug Prices

On September 30, 2009 the Special Committee on Aging held a hearing on reducing health care costs. As a follow up, Senator Kohl asked Senator Bill Nelson of Florida to chair a Special Committee on Aging hearing on March 17, 2010, "Seniors Feeling the Squeeze: Rising Drug Prices and the Part D Program,"[1] on the rising cost of drugs. At that hearing, Senator Kohl noted that Americans pay, on average, twice as much for prescription drugs as people in other developed countries. Further, the large discrepancies in the cost of identical drugs could not be explained by differences in production or manufacturing. Following the hearing, the Committee sent letters to AstraZeneca, GlaxoSmithKline, Eli Lilly, Novartis, Pfizer, and Sanofi-Aventis to ask about these discrepancies.

Letter to AstraZeneca: *www.aging.senate.gov/letters/drugcostsaz.pdf*
Letter to GlaxoSmithKline: *www.aging.senate.gov/letters/drugcostsgsk.pdf*
Letter to Lilly: *www.aging.senate.gov/letters/drugcostslilly.pdf*
Letter to Novartis: *www.aging.senate.gov/letters/drugcostsnovartis.pdf*
Letter to Pfizer: *www.aging.senate.gov/letters/drugcostspfizer.pdf*
Letter to Sanofi-Aventis: *www.aging.senate.gov/letters/drugcostssanofi.pdf*

These letters asked the following questions:

1. Why are there discrepancies between foreign and domestic prices for certain medications?
2. Have these prices changed in the past 10 years, and if so, why?
3. Ireland recently announced price reductions of 30 percent or more. Why are prices in Ireland, and other countries such as the Philippines being reduced, while prices continue to increase for U.S. consumers?
4. Manufacturers and industry representatives contended that U.S. pharmaceutical research is unparalleled, and accounts for a disproportionate share of needed innovation in pharmaceuticals and biologics. Despite the enormous investment made by the U.S. government and American consumers in pharmaceuticals, why aren't U.S. drug prices competitive when compared to the prices in other industrialized countries?
5. What percentage of your research budget is comprised of U.S. Federal funds?
6. What are your profit margins and distribution costs in each of the countries listed? What percentage of overall profit comes from the U.S.?

[1] Videocast and materials available at http://aging.senate.gov/hearing_detail.cfm?id=323166&.

7. Please list the number of employees in every country in which you employ them. What percentage of your operation is in the U.S.?
8. How much did your company spend on marketing each of these drug(s) in each country listed? How much was spent directly on marketing to physicians?
9. Did your company manufacture free samples of any of the aforementioned drug(s)? If so, please provide data on the cost associated with manufacturing and distributing these samples.

Findings: Detailed Questions and Responses

1. Why are there discrepancies between foreign and domestic prices for certain medications?

The companies were fairly consistent in their responses.

First, companies suggested that drug prices are higher in the U.S. than in other developed countries because other countries use price controls while the U.S. has a market-based system.

The respondents noted that foreign governments usually set prices in their countries. As Novartis said, "in other countries, where the government is the sole or majority provider of health care benefits, governments mandate the price of pharmaceutical products." Most companies also claimed that they prefer the U.S.'s market-based approach because it is more attractive to investors, leads to a stronger pharmaceutical industry, and allows prices to be set by market forces.

According to the manufacturers, foreign governments rely on price controls and formulary restrictions to ensure medications are affordable. As AstraZeneca stated in their reply, "pharmaceutical pricing reflects the policy choices and domestic market forces of this country."

Second, companies claimed that it was difficult to compare prices between countries because of the variety of requirements pharmaceutical companies face. GlaxoSmithKline said, "There are different regulations and market conditions in different countries which impact the pharmaceutical industry. These differences result in wide variations in labeling, manufacturing and packaging standards. Multinational pricing comparisons are extremely difficult as a result of these differences."

Several companies noted that the wholesale acquisition cost (WAC), which is the price cited in the Committee's letters to the companies, does not represent the net price paid by the purchaser. Novartis went so far as to say that "it is inaccurate and misleading to attempt to compare these foreign prices to WAC prices in the U.S., since WAC prices may not reflect the discounts offered or rebates paid." Aside from disputing the numbers used in the Committee's letter, Sanofi-Aventis noted that the Federal Supply Schedule, which sets prices for the Department of Veterans Affairs, Department of Defense, Indian Health Service and the Coast Guard, are derived from market prices.

2. Have these prices changed in the past 10 years, and if so, why?

Drug companies declined to clearly explain how and why drug prices changed over time.

The Committee found that U.S. prices are higher than foreign prices, and that they tend to rise more rapidly. The companies' responses provided a varying level of detail about the price disparities. Some offered fairly detailed tables, with the qualification that the pricing data they supplied was proprietary.

No company offered a business case for the setting or changing prices, other than mentioning the prices charged by rival products in the same drug class. The price rationales provided were vague, and referred to the differences in regulation between nations (see below). Some companies also noted the impact expiring patents would have on future prices as justification for current prices.

Several companies noted that the rate of increase in U.S. drug prices has declined in recent years.

3. Ireland recently announced price reductions of 30 percent or more. Why are prices in Ireland, and other countries such as the Philippines being reduced, while prices continue to increase for U.S. consumers?

Drug companies again pointed to the free-market approach in the U.S. versus the price control system in Europe as a problem in directly comparing prices.

The Committee's letters to the companies noted Ireland had recently announced reductions of 30 percent or more for many drugs, and that prices in the Philippines were much lower than U.S. prices.

The responses resembled the replies to the first question about why prices are lower in foreign markets. For example, Sanofi-Aventis wrote "[i]n contrast to the free market dynamics that dictate pricing in the United States, the governments in various countries in Europe play a significant role in setting prices." Eli Lilly wrote "[w]ith regard to the Philippines, it offers a particularly poor comparator to the United States. Its health care system is subject to widespread expressions of concern regarding the adequacy of access to the most basic of services for a clear majority of the population."

In addition, the policy changes that resulted in lower prices for some drugs did not apply to all the drugs about which the Committee asked. One company provided another cost methodology, "Net Wholesale Price," which indicated that prices for their drugs had increased in Ireland and the Philippines, though they still remained less than half of U.S. prices.

The companies also suggested other reasons why U.S. prices were appropriate. One company noted that with insurance subsidies, patients' out-of-pocket costs for their drugs were only 10 to 30 percent lower in foreign markets. Several others argued that the pricing policies of other nations lead to lower availability of innovative medications. AstraZeneca wrote, "…in Canada a

single government entity, the Patented Medicine Prices Review Board (PMPRB), regulates the prices charged by manufacturers for patented medications. Although recent changes to the PMPRB guidelines have created a more competitive pricing environment, a 2008-2009 study showed that only 55% of innovative medicines received approval from Canada's Health Technology Assessment appraisal system, compared to an international average of 73%."

4. Manufacturers and industry representatives contended that U.S. pharmaceutical research is unparalleled, and accounts for a disproportionate share of needed innovation in pharmaceuticals and biologics. Despite the enormous investment made by the U.S. government and American consumers in pharmaceuticals, why aren't U.S. drug prices competitive when compared to the prices in other industrialized countries?

See Question Above.

5. What percentage of your research budget is comprised of U.S. Federal funds?

Drug companies assert that they receive 0 to 1 percent of funding from the U.S. government for research. However, the companies did not take into account governmental programs that support innovation, including research programs, the patent system and tax preferences.

The companies all answered this question directly and reported little to no direct federal support—between 0 to 1 percent of their total research and development budget. Four of the six companies provided their overall research budgets, which varied from $4.4 billion to $10 billion.

Despite this purported lack of direct federal investment, pharmaceutical companies may benefit from government investment in training and research. Seventy-nine percent of drug and medicine patents cite the results of public science.[2] The Congressional Research Service[3] compiled several studies that found research funded by the National Institutes of Health (NIH) directly contributed to the development of four to nine percent of the top selling drugs studied. Specifically, CRS found two relevant studies:

> In response to congressional direction, the National Institutes of Health looked at 47 FDA-approved drugs that had sales of $500 million or more a year to determine the role of NIH-sponsored technologies in their development. As described in the resulting July 2001 report, *A Plan to Ensure Taxpayers' Interests are Protected*, "NIH sought to determine whether the agency, directly, or through a grantee or contractor, held any patent rights to the drugs."[4] NIH funded technologies were found to have been used in the development of four of these pharmaceuticals:

---

[2] Francis Narin, Kimberly S. Hamilton, and Dominic Olivastro, "The Increasing Linkage Between U.S. Technology and Public Science," *Research Policy*, 1997, 328. See also: G. Steven McMillan, Francis Narin, and David Deeds, "An Analysis of the Critical Role of Public Science in Innovation: The Case of Biotechnology," *Research Policy*, 2000, 1.

[3] Congressional Research Service. Federal R&D, Drug Discovery, and Pricing: Insights from the NIH-University-Industry Relationship. Wendy H. Schacht, Specialist in Science and Technology Policy January 6, 2010 (RL32324).

[4] *A Plan to Ensure Taxpayers' Interests are Protected*, National Institutes of Health, 2001. http://www.nih.gov/news/070101wyden.htm.

- Epogen® and Procrit® are based on different uses of a patented process technology developed at Columbia University with support from NIH grants. Columbia licensed their technology to Amgen for Epogen® and to Johnson & Johnson for Procrit®.
- Neupogen® is manufactured by Amgen using patented technologies for a process and a composition licensed from Memorial Sloan-Kettering Cancer Center (MSKCC). These technologies were developed with NIH grant support.
- Taxol® is manufactured by Bristol Myers Squibb (BMS) using a patented process technology developed by Florida State University (FSU) with NIH grant funds. In addition, the NIH has rights to an underlying technology arising from a NIH CRADA collaboration with BMS. The NIH has received from BMS tens of millions of dollars in royalties from FY1997 to FY2000 under the license to the NIH technology.

A 2003 study by GAO found that government financial support of extramural research and development had resulted in inventions that "were used to make only 6 brand name drugs associated with the top 100 pharmaceuticals that VA [the Veteran's Administration] procured for use by veterans and 4 brand name drugs associated with the top 100 pharmaceuticals that DOD dispensed in 2001."[5] What these, and other reports document is that "while NIH's federally funded research has contributed in a substantial, dramatic, yet general, way to advances in medicine and biology, the direct contributions to a final therapeutic product as a consequence of the Bayh-Dole process[6] is limited and difficult to determine."[7] In addition to multiple sources of innovation, tracking the federal contribution is made more difficult by the fact that the government does not retain ownership of inventions made by contractors.

These studies only capture research that leads to top-selling drugs. They do not capture other federally-supported efforts that do not result in a marketable drug. These research projects are also important to manufacturers, as they indicate which research directions will not be productive, thereby increasing the effectiveness and return of research investments made directly by manufacturers.

6. What are your profit margins and distribution costs in each of the countries listed? What percentage of overall profit comes from the U.S.?

Responses regarding profit and distribution costs in foreign markets were evasive and uninformative.

Expense information was included for one family of drugs, in which most of the expenses associated were related to marketing.

---

[5] General Accounting Office, *Technology Transfer, Agencies' Rights to Federally Sponsored Biomedical Inventions*, July 2003, GAO-03-536, 2.

[6] The Bayh-Dole Act, as implemented in 37 C.F.R. 401, gives intellectual property rights for inventions arising from federal research funds to the awardee institution, such as a university or small business.

[7] *A Plan to Ensure Taxpayers' Interests are Protected*, National Institutes of Health, 2001. http://www.nih.gov/news/070101wyden.htm.

Companies responded to the question as narrowly as possible, sometimes stating the drug was not marketed in all countries and was therefore impossible to compare. Answers ranged from no response to claims that over 80 percent of worldwide sales for specific drugs were made in the U.S.

One company provided a detailed response on one family of drugs, including information about one generic version, several new versions on patent, and a rival patented drug in same class owned by a different firm. Domestic sales in this class are in the multi-billion dollar range. For the patented versions owned by the responding firm, sales revenue exceeded brand expenses by 32.8 percent. Brand expenses included Manufacturing and Distribution (22.5 percent of revenue) and "Amortization of Intangibles," or the write-off for the declining value of the patent (9.7 percent of revenue). There were no research costs reported for the family of drugs in that calendar year. All other costs were associated with marketing (e.g. sales force, promotion, etc.).

U.S. Expenses and Sales in CY 2009 for a drug family, as supplied by one respondent[8]

Direct Brand Expenses	
Standard Costs (Manufacturing and Distribution)	(22 5%)
Cost of Goods Sold Variance	0.1%
Sales Force Expenses	(12.8%)
Promotion Expenses	(17.6%)
Marketing Management	(0.3%)
Medical Management	(0.2%)
Local Clinical Studies	0
Amortization of Intangibles	(9.5%)
G&A Allocation	(2.9%)
Marketing Administration	(0.7%)
Medical Administration	(0.9%)
Sales Less Direct Brand Expenses	**32.8%**

7. Please list the number of employees in every country in which you employ them. What percentage of your operation is in the U.S.?

Even though the U.S. represents the world's most profitable pharmaceutical market, almost all of these companies employed the majority of their workforce in foreign countries.

[8] Respondent emphasized that this table is not a profit and loss statement for its product and does not reflect the "profit" of product sales in 2009. Among other things, it does not include several indirect brand costs such as the costs of defending patents, defending product liability actions, transporting product doses from manufacturing sites, and researching and developing new products. The direct brand expenses also do not include taxes. For these reasons, the data above should **not** be considered a true reflection of product profitability.

Of the companies we questioned, we found the portion of U.S. based employees averaged 30 percent of all employees (ranging from 14 percent to 50 percent of employees). However, our review of these companies' annual reports and other financial disclosures reveal U.S. sales ranged from 32 percent to 45 percent of all sales.

Percentage of Employees in the United States

Company	% US Employees
Company A	25%[9]
Company B	23%
Company C	20%
Company D	50%
Company E	14%
Company F	45%

8. How much did your company spend on marketing each of these drug(s) in each country listed? How much was spent directly on marketing to physicians?

The companies provided different levels of granularity in their responses, either citing marketing costs for specific drugs or total overall marketing budgets.

Some companies reported marketing costs for individual drugs that varied from $80 million to $285 million per year worldwide. For those reporting overall marketing costs, they reported marketing and sales expenses between $8 and $11 billion per year worldwide.

9. Did your company manufacture free samples of any of the aforementioned drug(s)? If so, please provide data on the cost associated with manufacturing and distributing these samples.

Companies offered free samples and discounts, which were associated with marketing costs.

The companies noted that they offered free samples and direct-to-consumer discounts, some of which were based on the financial needs of the patient. Both of these efforts are counted as marketing costs, although they may not increase sales. Not all the companies listed the amount of free samples or discounts per drug for all of their products, but some volunteered that they provided hundreds of millions of dollars in free samples of all products, and hundreds of millions of dollars in discounts of their products to low-income or uninsured patients. [10]

[9] The percentage is for all North American employees.

[10] Limited price reductions can generate sales that might not have otherwise occurred at a higher price point, and encourage patient and physician use that extends beyond the discount period. For example, the Institute of Medicine found "[i]n academic medical centers, drug samples may be associated with the prescription of new brand name drugs in situations in which the sample drugs are different from the physician's preferred drug or are not recommended by evidence-based practice guidelines or in situations in which less expensive drugs or generic equivalents are available for the same indication."[10] Page 135. IOM (Institute of Medicine). 2009. *Conflict of Interest in Medical Research, Education, and Practice.* Washington, DC: The National Academies Press. Page 135. IOM (Institute of Medicine). 2009. *Conflict of Interest in Medical Research, Education, and Practice.* Washington, DC: The National Academies Press.

Conclusions

Drug prices are obscure

The Committee found pharmaceutical companies to be purposefully vague about pricing strategies within the U.S. market. Drug companies contend that the prices listed in our letters of inquiry may not be representative of actual prices paid by a purchaser, because they did not necessarily account for rebates, bulk discounts or other incentives. Companies said that the "true" prices vary by payer, are difficult to calculate, and are almost always privileged information. Further, publicly available drug price information is often inaccurate, and does not reflect the actual price paid by the purchaser or the consumer.

None of the data received demonstrated a direct relationship between prices charged and the costs of manufacturing, distribution, or research and development. Across the board, the largest expense category was always marketing.

U.S. Drug Prices Compared Internationally

Drug prices are higher in the U.S. because prices are market based, not governmentally negotiated. Drug companies set U.S. prices based on what the market will ultimately bear. Publicly held pharmaceutical companies also emphasized their fiduciary obligation to their shareholders to maximize their profit.

PART II. Investigation of Specific Drug Prices

In May 2011, Senator Kohl, along with Representatives Waxman, Pallone and DeGette, sent letters of inquiry to two pharmaceutical companies, URL Pharma and Avanir, regarding their two drugs, Colcrys and Nuedexta, respectively. Colcrys (colchicine) is prescribed as a treatment for gout and Familial Mediterranean Fever (FMF), and Avanir is prescribed as a treatment for pseudobulbar affect (PBA), which causes uncontrollable emotional outbursts and can accompany Multiple Sclerosis (MS) and Amyotrophic Lateral Sclerosis (ALS).

Each drug had previously been reported to be available as an "unapproved drug," which is a drug that has not been approved by FDA but is available commercially, though the Committee later learned that only one drug was widely available previously. In June 2006, FDA announced a new drug safety initiative to bring the roughly 2,000 unapproved drugs into the approval process.

Once the drugs were approved, their prices were many times higher than the reported cost of the unapproved drug. Both companies suffered negative attention from the media and Congress when these cost increases became public. This section summarizes the findings of the investigations into URL Pharma's and Avanir's pricing decisions. In the letters to the companies, they were asked about the costs of the clinical trials that led to approval; the determination of the list price, manufacturing and marketing costs; and, the patient access programs established to increase availability of the drug.

URL Pharma

The letter to URL Pharma asked about the pricing decision for Colcrys after media outlets reported that colchicine, the active ingredient, had been available for about $0.09 per tablet before FDA approval.[11] URL Pharma charges $4.85 per tablet of Colcrys, which is taken one to three times per day. The company spent $48 million to get Colcrys approved. After approval, URL Pharma petitioned FDA to take a strong stance against other single-ingredient colchicine applications, and clear the market of unapproved colchicine.

There were several items of note in URL Pharma's response. First, URL Pharma recognized that the federal government would be a major purchaser in the sale of Colcrys. According to the company, Colcrys revenues derived from Medicare (25%), Medicaid (4%) or other federal or state health care programs (20%) account for 49% of total revenues from product launch to April 2011.

Second, in response to the question about the determination of the sales price, URL Pharma submitted several presentations from outside consulting companies and internal notes. According to the documents, URL Pharma settled on the price of $4.85 after considering both substantially lower and higher prices recommended by outside contracting firms, and acknowledged that the higher price could result in pushback from the purchasing community.

Colcrys' labeling states that the company did not include enough seniors in their clinical trials to determine if they respond to Colcrys differently than younger patients. Despite this, the FDA found Colcrys to be safe and effective in the elderly at the time of approval, and allowed it to be dosed as such. In an internal memo on the pricing decision, URL Pharma tells its staff that one of Colcyrs' "core product messages" which "may be delivered through a variety of vehicles and may not be stated overtly" is that "Colcrys has been demonstrated to be safe and effective in elderly patients" (page 4300 – 4301).

While not necessary, considering that FDA found Colcrys to be safe and effective for seniors and allowed it to be dosed as such, URL Pharma elected to conduct an additional post-market study[12] to evaluate and compare the pharmacokinetics in young and old patients. This study found no difference in the pharmacokinetics of Colcrys, though the study included only three individuals over the age of 65 out of 18 elderly patients.

While investigating URL Pharma for pricing practices with regard to Colcrys, the Committee learned about URL Pharma's improvements to the unapproved drug. There were hundreds of adverse events and 169 deaths associated with the unapproved colchicine available on the market before FDA approved Colcrys.

---

[11] See, for example, Arthur Allen, "A Giant Pain in the Wallet: How drug companies are making crucial, common drugs up to 100 times more expensive," *Slate*, March 29, 2011 (http://www.slate.com/id/2289616/).

[12] Mutual Pharmaceuticals Company, Inc. Relative Bioavailability of Colcrys™ 0.6 mg Tablets in Healthy Young and Elderly Volunteers Under Fasted Conditions. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited July 20, 2011]. Available from: http://clinicaltrials.gov/ct2/show/NCT01001052 NLM Identifier: NCT01001052.

In 2006, FDA started the Unapproved Drug Initiative to clear the market of drugs that had never been approved, such as colchicine. URL Pharma answered FDA's call to conduct clinical trials on colchicine for its submission. In doing these clinical trials, URL Pharma discovered that a lower dosing regimen preserved the benefits of colchicine while minimizing harmful side effects. Still, some patients write that the lower dose schedule of the drug is less effective than previous unapproved versions; in a briefing for staff the company stated that these cases are inexplicable outliers. In addition, URL Pharma found several dangerous drug interactions, now included in Colcrys' label and the labels of several contraindicated drugs. FDA has commended these efforts.

The company has an extensive patient assistance program, and has helped over 50,000 patients thus far. The program provides benefits to patients earning up to 6 times the federal poverty level, and many patients receive the drug for free or for $5 per month's supply.

Avanir

The letter of inquiry to Avanir Pharmaceuticals concerned the pricing decision on their drug Nuedexta after media outlets reported that a combination of the drug's two active ingredients was available from compounding pharmacists for roughly $0.66 per day before FDA approved the drug, compared to $16 per day for Nuedexta. We found that the company invested heavily in the development of Nuedexta. It provided documents detailing expenditures of $239 million in overhead and research, and nearly all of its resources from 2009 to 2010 on developing the best proportion of ingredients and for testing.

Before Nuedexta, there was no approved treatment for PBA, which causes uncontrollable emotional outbursts in patients with MS and ALS; doctors previously treated PBA with powerful psychotropics used off-label. While some compounding pharmacist groups claim that the drug was indeed compounded[13], it appears that these instances were infrequent and could not have been the same safe and effective dosage that Avanir discovered. Avanir has suggested to staff that compounders started making the medication, which is comprised of two common and inexpensive ingredients, for former participants of Avanir's clinical trials after the trials ended. The company stated to staff in briefings that FDA treated the drug as a new entity.

The price of Nuedexta is slightly lower than the average (Wholesale Acquisition Cost of $16 per day, or $8 per tablet) of what consulting companies advised in 2010 (range between $6 and $43 per day, or between $3 and $21.50 per tablet). Notably, the company has told staff in briefings that the price was determined using a market-based approach, not based on expenditures, and that the company had lost money every year for 20 years prior to the approval.

Avanir Pharmaceuticals also has a co-pay assistance program. The drug entered the market in February 2011, and as of the end of June 2011, 343 patients have used this program.

Conclusion

[13] Angela Townsend, "Protests help bring down price for preterm birth drug Makena," *The Plain Dealer*, April 11, 2011 (http://www.cleveland.com/healthfit/index.ssf/2011/04/the_high_price_of_preventing_p.html).

From the recent investigation into URL Pharma and Avanir, we have learned that drug companies charge prices based mostly on what the market will bear without strong pushback from purchasers, and less on what the drug costs to develop, market or manufacture.