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Thank you, Senator Paul, and members of the Committee for the opportunity to provide testimony today regarding the rising medication prices in the US. The University of Kentucky's UKHealthCare (UK) operates two hospitals numbering 945 beds, several ambulatory clinics and six retail pharmacies, one of which is a specialty pharmacy. In FY16 UK saw 38K discharges, 1.29M outpatient visits, and UK Pharmacy Services dispensed 430K outpatient prescriptions.

The medication price increases seen recently, that have affected UK, can be classified into a variety of categories but for the purposes of this testimony will be placed into two basic groups, Direct/Obvious and Indirect/Less Obvious. The Direct/Obvious reasons include increase innovation, consequences of the Food and Drug Administration (FDA) Unapproved Marketed Drugs Initiative, changes in ownership, and the sole source effect. The Indirect/Less Obvious reasons are surrounding the Pharmacy Benefit Management (PBM) Impact.

Increases in Innovation

The majority of Increases in Innovation with medications can be generalized into the Specialty Pharmacy Phenomenon. Specialty medications now make up the majority of the drug development pipeline and within the last five years spend with specialty medications has doubled contributing to 70% of the overall medication spend between 2010 and 2015. The primary drivers for this growth were therapy developments in Hepatitis, autoimmune diseases, and oncology, which accounted for $19.3B in increased spend.[1] For example, in the case of Hepatitis C, in 2014 there was an increase of 742% in the cost of treatment as Sovaldi, Olysio and Harvoni entered the market. In 2015 the spend with Hepatitis C specialty improved with competition from newer agents (Technivie, Zepatier, and others) as well as more stringent insurer evaluations on appropriate use.[2] Another example is specialty medication developments in the field of Oncology, which has had much innovation and thus spend. This has been demonstrated with advances in immunotherapy and approaches with combination regimens such that annual costs for therapy approach $295K per a patient. These regimens have demonstrated significant increases in survival compared to traditional standards of care.[3, 4] With the proliferation of this specialty medication phenomenon, we will continue to see the cost of many new therapies remain expensive, which have a higher price ceiling than what is seen with non-specialty items.

FDA Unapproved Marketed Drugs Initiative

In 2006 the FDA announced its Unapproved Marketed Drugs Initiative with the goal of bringing medications that do not currently have FDA approval for marketing, due to a lack of safety and efficacy data, into compliance with the approval provisions of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) "without adversely affecting public health, imposing undue burdens on consumers, or unnecessarily disrupting the market."[5] To put this into historical context, in 1938 the FD&C Act was enacted due to the 107 deaths that resulted from mistaken ingestion of diethylene glycol. The purpose of this act was to ensure that medications were proven safe before use. Several drugs that were marketed before this act were grandfathered in (e.g. levothyroxine, digoxin, nitroglycerine, and phenobarbital). The 1962 Kefauver-Harris Amendment to this act was passed due to the serious birth defects seen with the tranquilizer medication, thalidomide. The purpose of this amendment was to

ensure that medications also be proven to be effective before use. This requirement was also extended to medications that received FDA approval between 1938 and 1962. The initiative, which includes Prescription and Over the Counter medications, has the potential to impact as many as 5,000 agents. Although the intent of this initiative was not to disrupt the market, this has not been the case for hospitals. Below are two case examples with the medications neostigmine and vasopressin:

Neostigmine: Observed price increase of 519% in three years.

- Originally patented in 1933 and approved in the US in 1939.
- Up until December 2013 there were a handful of generic Neostigmine products that never went through formal FDA safety and efficacy evaluations.
- December 2013 – Eclat funded studies to evaluate the use of what is already known with neostigmine and received formal FDA approval for reversal of non-depolarizing neuromuscular blocking agents after surgery.
    - FDA allowed time for other agents to enter the market.
- November 2015 – Price increased 127%
- January 2015 – Fresenius Kabi, following funded studies, received FDA approval to enter the market.
- February 2015 – Price increased further to 519%
- December 2015 – WestWard, following funded studies, received FDA approval to enter the market.
- End result: a handful of manufacturers making the same product used since the 1930s but there is a new average price that is 519% higher.
- **Impact**:
    - Compared to FY14, UK spent $243K more in FY15 and $259K more in FY16.
    - Measures were taken to modify use as much as possible.
    - The need for this agent has not changed; however, in absence of these efforts UK would have spent $700K more in the span of FY15 and FY16.

Vasopressin: Observed price increase of 3,362% in two years.

- First used as a vasopressor agent in the 1950s.
- Par Pharmaceuticals funded studies to evaluate the use of what is already known with vasopressin and received formal FDA approval for use in increasing blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines.
- November 2014 – Par gains approval and price increases to 1,137%
- April 2015 – As other generics begin to drop out of the market price increases 2,321%
- January 2016 – Price increases 2,787%
- July 2016 – Price increases 3,362%
- **Impact**:
    - Compared to FY14, UK spent $194K more in FY15 and $452K more in FY16
    - Measures were taken to modify use as much as possible.
    - The need for this agent has not changed; however, in absence of these efforts UK would have spent $800K more in the span of FY15 and FY16.

Change in Ownership Effect

Over the last few years a shift in the markets with generic medication price increases has gained much attention in the press. This is largely for the impact it has had on patients in the retail setting and the

barriers that have come with making much needed medications unaffordable. The most notable examples have been seen with Mylan's EpiPen and Turing's Daraprim. This change in ownership effect has also been observed with medications that are largely used in hospitals, however, given that these medications are not dispensed in a fee-for service environment, public awareness to the extension of this issue is low. Unlike the examples listed above with the FDA initiative, the manufacturers of these generic medications have not invested dollars into research of the medications' safety and efficacy profiles. Below are 2 case examples with nitroprusside injection and calcitonin injection to demonstrate the financial impact of this effect on UK. Nitroprusside is used for the immediate reduction of blood pressure in hypertensive crises, for producing controlled hypotension to reduce bleeding during surgery, and for the treatment of acute congestive heart failure. Calcitonin is used for the early treatment of hypercalcemic emergencies.

Nitroprusside Injection: Observed price increase of 1,745% in less than two years.

- Since 1988 Hospira has owned and produced.
- December 2013 – Marathon acquired and the price increased 350%.
- February 2015 – Valeant acquired and price increased 1,250%.
- July 2015 – Valeant increase price 1,438%.
- August 2015 – Valeant increased price 1,745%.
- **Impact**:
    - Compared to FY14, UK spent $194K more in FY15 and $104K more in FY16.
    - Measures were taken to modify use as much as possible.
    - The need for this agent has not changed; however, in absence of these efforts UK would have spent $100K more in the span of FY15 and FY16.

Calcitonin Injection: Observed price increase of 3,259% in a little over three years.

- Since 1986 Sebela has produced this product.
- August 2014 – Increased price 1,258% (from the price in January 2013)
- September 2015 – Mylan acquired the product
- March 2015 – Increased price 2,823%
- May 2016 – Increased price 3,259%
- **Impact**:
    - Compared to FY14, UK spent $451K more in FY15 and $390K more in FY16.
    - Measures were taken to modify use as much as possible.
    - The need for this agent has not changed; however, in absence of these efforts UK would have spent $1.5M more in the span of FY15 and FY16.

It should be noted that in addition to the impact on medication spend, this has also led to a need for increased resources to manage. Both the FDA initiative and the change in ownership effect led UK to create a pharmacist role responsible for overseeing larger medication utilization initiatives two years ago. This role, filled by Dr. Jeremy Flynn, has been key in monitoring for price spikes, identifying current use of affected medications, gaining consensus from providers on how we can modify use (supported by evidence based literature), and monitoring utilization moving forward. What is not known and has not been measured is the clinical outcomes associated with these practice changes. This month UK will be sending Dr. Flynn to Chicago for advanced analyst training so that outcomes can be measured in conjunction with these increasing utilization initiatives.

Sole Source Effect

A phenomenon that has been reported in the retail environment over the last two years is a sole source effect seen with many generic medications. The medications that are being affected by this are typically older therapies and have been somewhat replaced by novel therapies. With diminishing interest in these generic medications and manufacturers looking to invest in innovative new therapies, several generic manufactures are leaving this market. The result is that there may be one or two remaining manufacturers. When this occurs, price increases are not uncommon. Below is a table of medications reported by Vizient Inc. that have observed sharp price increases as a result of this sole source effect:[6]

Generic Medication	Percent Price Increase 2014-2015
Hydroxychloroquine 200 mg tablet	1,245
Fluoxetine HCl 10 mg tablet	1,131
Atenolol 50 mg tablet	803
Propranolol 40 mg tablet	783
Digoxin 125 mcg tablet	681

It should be noted that this is similar to the impact often seen with medication shortages as generic injectable medications have seen drastic price increases when shortages occur.[7]

A potential solution to some of the Direct/Obvious reasons listed above include S. 3335: Fair Accountability and Innovative Research (FAIR) Drug Pricing Act of 2016, introduced on September 15, 2016 by Sen. Baldwin (WI). This bill contains language that would require manufacturers of certain drugs and biological products to report to the Department of Health and Human Services that result in a 10% or more increase in price over a twelve month period.

Additionally, consideration should be given by the FDA on the analyzing the market impact of their Marketed Unapproved Drugs Initiative thus far. If the two medication examples listed above increased expenses of in excess of $1M in a two year span of time for a single health system, then careful consideration should be given to the approach of this initiative as others in the potential denominator of 5,000 are considered.

Pharmacy Benefit Manger Impact

During the Full House Committee on Oversight and Government Reform hearing on EpiPen, Heather Bresch, CEO of Mylan, stated that although the cost of the 2-pen EpiPen is $608, Mylan only receives $274 net revenue on the transaction.[8] Questions should be asked as to where the remaining $334 goes. It is likely shared between the wholesaler, insurer, pharmacy, and PBM. Lack of transparency will obscure where every dollar goes, however, given the rapidly increasing profits of the larger PBMs, it is not unlikely that they are receiving the majority of this.

PBMs are the middle men of sorts in the prescription drug industry coordinating the sale and reimbursement of prescription drugs between health insurance plan sponsors or employers, drug manufacturers, and local and national pharmacies. PBMs started out in the 1970s as entities that mostly performed claims processing. Much has changed over the years as PBMs now largely control the flow of medication from manufacturers to patients, control the formularies of covered medications, control the reimbursement amounts provided to pharmacies for dispensing medication and other related therapy management and counseling services, and run their own mail order and specialty pharmacies, which many patients are often required to use under certain plan designs. PBMs do provide valuable services,

such as their touted ability to gain reductions in medication costs for plans and employers, provide national pharmacy access, and facilitate pharmacy benefits for a wide variety of clients.[9] Despite these benefits some of the concerns with the evolved state of PBMs as it relates to rising medication costs are the considerable consolidation of the PBM market coupled with unprecedented growth, the lack of transparency in PBM operations and finances, and the PBM ownership of mail order and specialty pharmacies.

The PBM market in the US has undergone rapid consolidation to the point that it resembles an oligopoly. In 2012 the Federal Trade Commission (FTC) permitted Express Scripts Inc. (ESI) to acquire Medco (the two largest PBMs in the US at the time), thus forming the largest specialty pharmacy, Accredo. Then in March 2015 the FTC allowed United/Optum's acquisition of Catamaran (the third and fourth largest PBMs) to form OptumRx. Finally, in July 2015 the FTC allowed CVS Caremark (the largest PBM for Medicare Part D plans) to acquire Omnicare (the largest long-term care pharmacy), which is heavily reliant on Part D patients. This consolidation has led to three large PBMs (ESI, CVS Caremark and OptumRx) controlling approximately 80% of the PBM market. Parallel to the consolidation, the two largest of these PBMs (ESI and CVS Caremark) have demonstrated a profit increase from approximately $900M to $6B (600% increase) in a span of ten years.[10]

The lack of transparency with what is occurring with rebates (as mentioned in the EpiPen hearing) and payments at the transactional level (adjudication and beyond) coupled with this consolidation and growth of the PBM industry has led many in the retail pharmacy business to question the practices of the PBMs. The advent of Direct and Indirect Remuneration (DIR) fees (a.k.a. "Clawbacks") has extended the timeframe for the dispensing transaction to take place long after the adjudication (sometimes weeks or months) so that PBMs can charge additional fees after the transaction making it difficult for pharmacy owners to determine profitable dispenses. Additionally, the pricing structure of many pharmacy contracts with PBMs is not transparent with regards to the Maximum Allowable Cost or MAC, making the MAC for many PBM agreements a moving target. In response, the industry is developing tools for pharmacies to monitor transaction payments from PBMs for any deviations in the MAC. However, even with the use of such tools, PBMs make it difficult for pharmacies to appeal incorrect MAC pricing claims.

Tied into the rising price of medications is the PBM ownership of mail order and specialty pharmacies. PBMs are tasked with managing drug costs for health plans and employers by maintaining a formulary. However, if the PBM owns a pharmacy, will the PBM prefer medication A which is effective or medication B which is also effective but could have a better rebate and the cost of paying a pharmacy at the transaction level for the medication is irrelevant because it is owned by the PBM?

This strong link between the PBMs and their owned pharmacies has had a direct impact on UK's specialty pharmacy in day to day management of patients. UK has had patients who wished to have their specialty medications filled with UK Specialty Pharmacy. In the process of completing the fill a Prior Authorization (PA) is often required. This involves contacting the PBM to make a case for approval of the therapy and often involves engaging the medical team, providing labs, and sharing information on previously failed therapies. Following the PA being issued by the PBM, UK pharmacy staff have learned to act promptly as there have been numerous instances where the PBM-owned pharmacy contacts the clinic staff via phone and asks for a duplicate prescription to be sent. Early on in UK's specialty pharmacy operation PBM-owned pharmacies could capture specialty prescription by this method; however, after much discussion with clinic staff over the frustrated patients who were forced to wait for their medication to be dispensed from a pharmacy states away, this PBM strategy has not been as successful.

It is likely that this strategy has been successful in other pharmacy settings which simply do not have the resources to combat this conduct.

There are several potential solutions to making this contributing sector to the true price of medications more transparent. H.R. 244: MAC Transparency Act (only pertains to Medicare), introduced on January 9, 2015 by Rep. Doug Collins (GA). This bill contains language that would prohibit PBMs from transmitting patient information (including claims data) to PBM-owned pharmacies unless the plan enrollee voluntarily elects to allow this, and require PBMs to define and disclose MAC to participating Pharmacies, to identify the source for this calculation, to not update any more frequently than 7 days, and to establish a dispute resolution process for reimbursed claims that are below the acquisition cost. S. 3308: Improving Transparency and Accuracy in Medicare Part D Spending Act, introduced on September 12, 2016 by Sen. Shelley Capito (WV), will allow for greater transparency at the claim level between retail pharmacies and PBMs as it will prevent Clawbacks from occurring and will require PBMs to be transparent about fees at the adjudication.

Conclusion

In closing I am pleased to see that legislation has been introduced to address the Direct/Obvious and Indirect/Less Obvious reasons for the medication price increases we have seen. It is my hope that public awareness of this issue in the retail environment will be extended to the hospital environment for the reasons listed above.

Thank you, again, for the opportunity to provide testimony today. I am happy to answer any questions you have.

References:

1. Medicine Use and Spending in the US. IMS Institute. April 2016
2. Express Scripts 2015 Drug Trend Report.
3. Helwick C. Cost of Immunotherapy Projected to Top $1 Million per Patient per Year. ASCO Post. July 10, 2015.
4. Loftus P. FDA Approves Merck's Keytruda for Most Common Form of Lung Cancer. *WSJ*. October 2, 2015.
5. Guidance for FDA Staff and Industry. Marketed Unapproved Drugs – Compliance policy Guide. September 19, 2011.
6. Lucio S, Birt A. Understanding Escalating Drug Prices and Mitigation Strategies. Vizient Webex. September 20, 2016.
7. Erstad BL. Value-Based Medicine: Dollars and Sense. *Crit Care Med*. 2016 Feb;44(2):375-80
8. Testimony of Heather Bresch. Reviewing the rising price of EpiPens. Before the House Committee on Oversight and Government Reform. September 21, 2016.
9. Jorgenson J, Zappa A. Is PBM Transparency an Answer to Controlling Rising Drug Costs? *Am J Pharm Benefits*. 2015;7(4):161-164
10. Testimony of David A. Balto. The State of Competition in the Pharmacy Benefits Manager and Pharmacy Marketplaces. Before the House Judiciary Subcommittee on Regulatory Reform, Commercial and Antitrust Law. November 17, 2015.

Summary Biography

Dr. Philip Almeter is the Senior Director of Pharmacy Acute Care Services at the University of Kentucky's UKHealthCare (UK). Dr. Almeter received his Doctor of Pharmacy from the University of Georgia in 2009. While at the University of Virginia (UVa) he completed an ASHP accredited PGY1 Pharmacy Residency in 2010 followed by an ASHP accredited PGY2 Health System Pharmacy Administration (HSPA) Residency in 2011, when he served as Chief Resident. Following residency Dr. Almeter managed Supply Chain, Financial Services, and OR Services for the UVa Department of Pharmacy for a year before joining the Pharmacy Department at UK. Dr. Almeter has served in roles including the Director of Operations and Business Development and the Director of Acute Care Services and 340B Programs prior to his current role. Current responsibilities include overseeing the health system annual pharmacy supply chain spend ($180M), Pharmacy Operations and Clinical Pharmacy Services for Chandler Hospital, Good Samaritan Hospital, the Markey Cancer Center, and other UK clinics; 340B program oversight and compliance, and residency program director for the UK PGY1/PGY2 HSPA Residency. Dr. Almeter is a voting member of the UK Pharmacy and Therapeutics Committee and has served as a member of the Vizient University Health System Consortium Business of the Pharmacy Enterprise Committee for 2.5 years. Research interests include Supply Chain, 340B, Benchmarking, and Pharmacy Benefit Mangers. Recently Dr. Almeter presented a manuscript for publication with other colleagues at UK regarding the rising drug costs seen in the hospital environment. The review article titled, Managing the Rising Costs and High Drug Expenditures in Critical Care Pharmacy Practice, has been accepted for publication in the peer reviewed journal Pharmacotherapy and is currently in press.