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EPIPEN PRICE INCREASES: HOW REGULATORY BARRIERS INHIBIT PHARMACEUTICAL COMPETITION

FIELD HEARING

OF THE

SUBCOMMITTEE ON CHILDREN AND FAMILIES

OF THE

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS

UNITED STATES SENATE

ONE HUNDRED FOURTEENTH CONGRESS

SECOND SESSION

ON

EXAMINING EPIPEN PRICE INCREASES, FOCUSING ON HOW REGULATORY BARRIERS INHIBIT PHARMACEUTICAL COMPETITION

OCTOBER 7, 2016 (Lexington, KY)

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C O N T E N T S

STATEMENTS

FRIDAY, OCTOBER 7, 2016

EPIPEN PRICE INCREASES: HOW REGULATORY BARRIERS INHIBIT PHARMACEUTICAL COMPETITION

FRIDAY, OCTOBER 7, 2016

U.S. SENATE,
SUBCOMMITTEE ON CHILDREN AND FAMILIES,
COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS,
Lexington, KY.

The subcommittee met, pursuant to notice, at 2:57 p.m., at the University of Kentucky College of Health Sciences, Charles T. Wethington, Jr. Building, Commons Room, 900 South Limestone Street, Lexington, KY, Hon. Rand Paul, chairman of the subcommittee, presiding.

Present: Senator Paul.

OPENING STATEMENT OF SENATOR PAUL

Senator PAUL. Hello. Welcome. Thank you for coming. The Senate Committee on Health, Education, Labor, and Pensions Subcommittee on Children and Families will please come to order.

This afternoon, we're having a hearing on EpiPen price increases. It's important when you get upset about something or when you see a problem that you try to scratch beyond the surface and see what the origin of the problem is and try to fully understand it before we react and try to fix it.

I'd like to thank the University of Kentucky, the UK College of Pharmacy, and UK Healthcare for hosting this subcommittee hearing.

When I first heard about the EpiPen price increases going up 500 percent, I was like anybody else, outraged. I have allergic reactions to bees and have had to use epinephrine when I was a kid. Many families have that sort of experience, and they hate to think of sort of a lifesaving drug having a—they just don't understand why it costs 500 percent more, particularly when the ingredients are quite inexpensive.

The ingredients—epinephrine has been around for maybe 100 years. It's about a dollar's worth of medication in there, and people—some have tried to say, "Well, it's a complicated device." They haven't really been in a modern hospital if they think a spring loaded needle is a complicated device.

We've been exploring the question. We've had the FDA come in. We won't have them represented here today. It's kind of hard to get bureaucrats out of Washington. We have interviewed them in

the office, and we have some serious questions. Some of these questions we will discuss here with the panel.

One, they have a patent, and I'm for patents. That's intellectual property. It's one of the reasons why the great developers of things that require patents are intellectual property, like drugs. We're a leader in creating new drugs, innovative drugs. That's great. Patents can't last forever, and their patent will run out in 2025. They got it in 1987, a 38-year patent. My understanding is that an original patent is about 20 years. How did it get to be 38 years?

We want to know why there's no competition. Why is there only one person selling these? There is a generic. There's many different generics, but there's at least one generic that applied 7 years ago. Is it a little too long to have the government take 7 years to approve things? Why does it take so long, and what can we do to speed up the process?

We ought to think about how long patents should be. We ought to think about how long the process should be. Then we ought to think about how other countries do it and whether or not some other countries do it more quickly.

One of the bills that we've introduced says if it's been approved in Europe, and it's on the general market, and there hasn't been any significant health or safety problems with it, then maybe we can dispense with the Phase 1, Phase 2, Phase 3 trials and go directly to a committee that would still review the information, review it for safety and efficacy, but maybe not make the company start over, and that we could expedite this. Or maybe we should expedite things when there's only one person making something and the price goes up at an alarming pace.

There are a lot of good ideas. We have some patients in the audience who have allergies and have to buy the EpiPen. We have people who are involved with pharmacies selling the medication. We have economists and policymakers.

Without any further ado, we're going to start by going around, and you can either make an opening statement or you can introduce yourself and make an opening comment, but I'm going to give you your choice, and then we'll proceed from there. I'll begin by introducing Laura Jackson, who is the coordinator of the Kentucky Families With Food Allergies support group.

Laura.

Ms. JACKSON. Thank you for inviting us today. I hope I can give you a good perspective on what parents and families are going through.

Senator PAUL. Thank you. If you want to make any more comment than that, you can. We'll come back in a question and answer, but go ahead if you——

Ms. JACKSON. So I should go ahead?

Senator PAUL. Yes. If you have a statement, go ahead.

STATEMENT OF LAURA JACKSON, COORDINATOR, KENTUCKY FAMILIES WITH FOOD ALLERGIES SUPPORT GROUP, LEXINGTON, KY

Ms. JACKSON. I have been a food allergy parent for over 25 years, raising two sons with life-threatening food allergies. I know all too well the dangers of a severe allergic reaction, having witnessed it

with my own child, watching my son's symptoms progress from mild to severe in a matter of seconds, seeing his labored breathing, the panic in his eyes, racing to the emergency room and wondering if we could get there in time, knowing that a tragedy was possible, living with the fear of it happening again, and then worrying at every meal.

These experiences inspired me to form the Kentucky Families With Food Allergies support group here in Lexington 10 years ago. There are many parents like me in our State, all facing the financial and emotional responsibilities that come from raising a child with a life-threatening condition. That is why Kentucky's food allergy parents are so concerned about the current EpiPen price increases.

For over 15 years, my family purchased between 8 and 10 EpiPen two-packs per year for our sons who are now grown. We needed that many due to expiration dates and also to ensure that the injectors would always be within reach at home, when traveling, or at school, because prompt administration can make the difference between life and death.

In 2013, we were thrilled to have a new option when the Auvi–Q injector came onto the market. It was compact and much more user friendly. We switched to the Auvi–Q when it was first introduced. In 2013, it cost my family roughly the same amount as the EpiPen injectors. Soon after, the EpiPen manufacturer began offering significant discounts so that EpiPens were less expensive than Auvi–Q. Then Auvi–Q offered discounts. I saw the cause and effect. Now that EpiPen had a competitor, they found a way to lower the price.

Two years later, in July 2015, our insurance changed to a nearly unreachable $5,000 deductible. We began paying the cash price. At that time, our cost for an EpiPen two-pack or an Auvi–Q two-pack was virtually the same, about $390.

Within a few months, there was a dramatic change in price. In October 2015, Auvi–Q was recalled, and 2 months later, our cost for an EpiPen two-pack shot up to well over $600. That was an increase of over $200. Since our insurance had not changed, I believe that the manufacturer was responsible. When I asked my pharmacist why the price had increased so dramatically, he said, "They are the only game in town." It is my feeling that if Mylan had competition, the price would drop.

Last year, we went looking for an alternative and were pleased to find the Adrenaclick generic auto injector that cost us $116 for a two-pack. It works a little differently than the EpiPen and is not an exact generic, and, therefore, my pharmacy and my allergist had never mentioned it.

I believe the other reason that the Adrenaclick was never prescribed for my sons is the product's sporadic availability. Adrenaclick is manufactured by the American company, Amedra Pharmaceuticals. At various points in time over the last several years, Amedra Pharmaceuticals has not been able to keep up with the demand. The situation is confusing for all involved, pharmacies, physicians, and consumers. Assuming the supply catches up soon, how do we make sure that consumers are aware of this lower-cost option?

My local school system is also affected. They tell me that fewer parents are sending EpiPens to keep at school due to the cost. This creates a dangerous situation. In Fayette County, each building has four stock EpiPens for emergency use. They are intended to be a safety net for the undiagnosed or for students whose own EpiPen is for some reason not available. Those EpiPens stay in the building. That means students are riding on buses without EpiPens, going on field trips without EpiPens, walking home without EpiPens.

In addition, an average of one in 13 children now have a food allergy, which is roughly 2 per classroom. The school's four stock EpiPens cannot possibly protect the entire student population. Parents need to continue to supply EpiPens for children with documented food allergies, but with skyrocketing costs, many parents can't. The high cost is putting children at risk.

There are many families in our local support group who are struggling with this issue. Some parents are keeping EpiPens past the expiration date. Some parents are doing without. Many parents have told me that they are frustrated that one company has so much control.

We need this lifesaving medication to be sold at a reasonable price so that every child can be safe. Please allow more manufacturers to produce epinephrine injectors.

[The prepared statement of Ms. Jackson follows:]

PREPARED STATEMENT OF LAURA JACKSON

My name is Laura Jackson, and I have been a food-allergy parent for over 25 years, raising two sons with life-threatening food allergies.

I know all too well the dangers of a severe allergic reaction, having witnessed it with my own child. Watching my son's symptoms progress from mild to severe in a matter of seconds—seeing his labored breathing—the panic in his eyes—racing to the emergency room and wondering if we could get there in time—knowing that a tragedy was possible—living with the fear of it happening again—worrying at every meal.

These experiences inspired me to form the Kentucky Families with Food Allergies support group here in Lexington 10 years ago. There are many parents like me in our State, all facing the financial and emotional responsibilities that come from raising a child with a life-threatening condition. That is why Kentucky's food allergy parents are so concerned about the current EpiPen price increases.

For over 15 years, my family purchased 8 to 10 EpiPen two-packs per year for our sons who are now grown. We needed that many due to expiration dates, and also to ensure that the injectors would always be within reach at home, when traveling, or at school, because prompt administration can make the difference between life and death.

In 2013, we were thrilled to have a new option when the Auvi-Q injector came onto the market. It was compact and much more user-friendly, so we switched to the Auvi-Q when it was first introduced. In 2013, it cost my family roughly the same amount as the EpiPens injectors. Soon after we had already filled our prescription, the EpiPen manufacturer began offering significant discounts so that EpiPens were less expensive than Auvi-Q. Then, Auvi-Q offered discounts. I saw the cause and effect: now that EpiPens had a competitor, they found a way to lower the price.

Two years later in July 2015, our insurance changed to a nearly unreachable $5,000 deductible, so we began paying the cash price. At that time, our cost for an EpiPen two-pack or an Auvi-Q two pack was virtually the same at about $390.

Within a few months, there were dramatic changes in price. In October 2015, Auvi-Q was recalled, and 2 months later our cost for an EpiPen two-pack shot up to well over $600. That was an increase of over $200. Since our insurance had not changed, I believe that the manufacturer was responsible.

When I asked my pharmacist why the price had increased so dramatically, he said, "They are the only game in town." It is my feeling that if Mylan had competition, the price would drop.

We went looking for an alternative. Unfortunately, there is no exact alternative. We opted to purchase a generic epinephrine injector, called Adrenaclick, that cost us $116 for a two-pack, but it is not an exact substitute. That is why the pharmacy won't automatically substitute one for another. Some consumers might find the generic harder to use. In addition, many parents are not aware that Adrenaclick is available. EpiPen is well-known due to their advertising and marketing campaigns, but there is no marketing for the generic. That is another issue to address: how do we make sure consumers are aware of this lower-cost option?

My local school system is also affected. They tell me that fewer parents are sending EpiPens to keep at school, due to the cost. This creates a dangerous situation. In Fayette County, each building has four stock EpiPens for emergency use, but they are intended to be a safety net for the undiagnosed or for students whose own EpiPen is not available. Those EpiPens stay in the building. That means students are riding on busses without EpiPens, going on field trips without EpiPens, walking home without EpiPens, going to sporting events without EpiPens. The high cost is putting children at risk.

There are many families in our local support group who are struggling with this issue. Some parents are keeping EpiPens past the expiration date. Some parents are doing without. Many parents have told me they are frustrated that one company has so much control. We need this life-saving medication to be sold at a reasonable price so that *every* child can be safe. Please allow more manufacturers to produce epinephrine auto-injectors.

Senator PAUL. Thank you, Ms. Jackson.

John Spencer is an independent pharmacist and the owner of Spencer Drugs.

STATEMENT OF JOHN SPENCER, PharmD, INDEPENDENT PHARMACIST, OWNER, SPENCER DRUGS, RICHMOND, KY

Mr. SPENCER. Thank you, Senator Paul. As you said, my name is John Spencer, and I graduated from the University of Kentucky College of Pharmacy in 1992. I have worked in an independent pharmacy since 1989, and I currently own four independent pharmacies. My staff and I are literally on the front lines of patient healthcare and provide education and information that is necessary for our patients to take their medications correctly in order to maximize their effectiveness in their treatment.

Unfortunately, in the past few years, we find that we have become arbitrators between pharmaceutical manufacturers, pharmacy benefit managers, insurance companies, and patients. Too often, we have to attempt to explain huge price increases and formulary changes to a person that is sick and often in need of potential lifesaving medication. As you might imagine, these excuses are hard to come by. When talk of multimillion-dollar salaries for drug company executives is all over the news, it is really hard for my patients to understand when the price of their prescription increases by 500 percent.

I am a businessman, and I understand the free market. However, in the pharmaceutical industry, there are too many players with the ability to manipulate the system, and that is not at the heart of true capitalism or reasonable business ethics. I also understand that the pharmaceutical companies with proprietary products need to make a profit and be paid for their research. It appears that, in many cases, these companies are choosing an increase in their stock price over an increase in accessibility to those who need the treatment the most.

This industry has to be put under a different microscope when we evaluate their pricing practices. We're not dealing in sporting goods or appliances. We're dealing with products that can mean life and death for our patients.

It is an inconvenient truth for the makers of EpiPen when we tell them about a local teacher with severe peanut allergies who finds out that her co-pay for her EpiPen is now $250. The last time I checked, most school teachers are not highly compensated, and the idea of having to replace this product year after year is not a pleasant thought.

Mylan does not want to discuss about a mother from Tennessee whose child was starting kindergarten this year. She couldn't believe the price she had heard from her local pharmacy, so she started calling pharmacies in Kentucky in hopes of finding a cheaper price. Heather Bresch might be uncomfortable hearing about my colleague's patient with alpha-gal allergy whose insurance co-pay was $626 because her deductible had to be met.

Currently, you can go online to EpiPen.com and apply for a co-pay discount card, which may take up to $300 off your prescription in certain instances. In my two decades of work in pharmacy, I have no memory of any co-pay card offering such a staggering discount. What I know is that if you can afford to offer a $300 discount, there's at least a $300 profit in your product.

A 30 cc vile of epinephrine, as the Senator was mentioning, which contains enough drug to make several EpiPens—probably in the neighborhood of 20—costs me $58.99. Therefore, it's really hard to believe that the active ingredient has a significant bearing on the cost of the product.

Lawsuits, citizens' petitions, and back-door payment deals between brand manufacturers and generic companies that are about to launch their product seem to be the norm. I guess this explains why some pharmacy benefit managers still choose to pay for products like Nexium and Crestor long after AB-rated generics exist, even though they are sometimes less than 5 percent of the cost of the brand name drug.

On Mylan's Web site under the heading, Integrity, "Doing what's right is sacred to us. We behave responsibly, even when nobody is looking. We set high standards from which we never back down." My response to that would be everyone is now looking, and we expect more responsible behavior.

Thank you, Senator.

[The prepared statement of Mr. Spencer follows:]

PREPARED STATEMENT OF JOHN SPENCER, PHARMD

Senator Paul, my name is John Spencer and I graduated from the University of Kentucky College of Pharmacy in 1992. I have worked in independent pharmacy since 1989 and I currently own 4 independent pharmacies. My staff and I are literally on the front lines of patient health care and provide the education and information that is necessary for our patients to take their medications correctly in order to maximize their effectiveness in their treatment.

Unfortunately in the past few years, we find that we have become arbitrators between pharmaceutical manufacturers, pharmacy benefit managers, insurance companies and patients. Too often we have to attempt to explain huge increases in prices and formulary changes to a person that is sick and often in need of a potential life-saving medication. As you might imagine, those excuses are hard to come by. When talk of multi-million dollar salaries for drug company executives is all over the news, it is really hard for my patients to understand when the price of

their prescription increases by 500 percent. I am a businessman and I understand the free market, however in the pharmaceutical industry there are too many players with the ability to manipulate the system and that is not at the heart of true capitalism or reasonable business ethics. I also understand that pharmaceutical companies with proprietary products need to make a profit and be paid for their research. But it appears that in many cases these companies are choosing an increase in their stock price over an increase in accessibility of their product to those who need their treatment the most.

This industry has to be put under a different microscope when we evaluate their pricing practices. We are not dealing in sporting goods or appliances. We are dealing with products that can mean life or death for our patients.

It is an inconvenient truth for the makers of EpiPen when we tell them about a local teacher with severe peanut allergies who finds out that the copay for her EpiPen is now $250. The last time I checked most schoolteachers are not highly compensated employees and the idea of having to replace this product every year is not a pleasant thought.

Mylan does not want to talk about the patient from Tennessee we heard from whose child was starting kindergarten that couldn't believe the price that was quoted by her local pharmacy and was calling to see if she might find a better price in Kentucky.

Heather Bresch might be uncomfortable hearing about my colleague's patient with Alpha Gal allergy whose insurance copay was $626.16 because her deductible had to be met.

Currently you can go online to www.epipen.com and apply for a copay discount card which may take up to $300 dollars off your prescription in certain instances. In my two decades of work in a pharmacy I have no memory of any copay card offering such a staggering discount. What I do know is that if you can afford to offer a $300 discount there is at least a $300 profit built into your product.

On Mylan's Web site under the heading "integrity" it reads, "Doing what's right is sacred to us. We behave responsibly, even when nobody is looking. We set high standards from which we never back down." My response to that would be . . . everyone is now looking and we expect more responsible behavior.

Thank you Senator Paul for your time and for your concern about this issue.

Senator PAUL. Our next witness is Professor Brian K. Strow, Ph.D., who is a Professor of Economics at Western Kentucky University in my hometown of Bowling Green and a BB&T Professor for the Study of Capitalism.

STATEMENT OF BRIAN K. STROW, Ph.D., BB&T PROFESSOR FOR THE STUDY OF CAPITALISM, PROFESSOR OF ECONOMICS, WESTERN KENTUCKY UNIVERSITY, BOWLING GREEN, KY

Mr. STROW. Thank you, Senator Paul, for inviting me to testify before this committee today. I value any opportunity I have to talk about the values of competition, generally, and in this case, specifically, as it applies to the pharmaceutical industry.

My comments today will revolve around the value of competition, generally, to markets and to consumers, specifically, evident—I'll show some evidence of that value in the pharmaceutical industry, specifically; explain barriers to this competition, generally, and why they might occur in general scenarios and also, specifically, why they're occurring in these specific drug markets; and then at the end, suggest some policy solutions that we might look at addressing the very specific barriers to competition.

To economists, we generally find that competition is good and more competition is better. Why is that the case, and why do consumers value choice? It's because they gain power in the economic transaction. If there's only one producer, a monopoly producer can charge a lot more than if there's a competitor out there. If I'm willing to pay $10 for a drug, and I'm able to pay $10 for a drug, and

they charge me $10 for a drug, that transaction will occur, but I've got no, in economic terms, consumer surplus. I get no extra benefit out of making this purchase.

If the price of drugs fall—and we'll look at how this happens through competition—say, to $4, if I'm still willing to pay $10 and only have to pay $4, in economic language, I'd be gaining $6 of consumer surplus. What we look at as benefits to society—we're going to add up, as economists, these consumer surpluses, freeing up, as it were, people's incomes to spend on meeting other needs and wants.

The FDA actually comes in very handy here, because in 2005, they did a very specific study regarding the benefits of competition in the pharmaceutical industry. What they did was look between 1999 and 2004 at average drug prices and compared it to the number of competitors in each specific drug market, so if there were two drug makers, three drug makers, one drug maker, five, six—they took it out to double digits.

What is interesting when you see the study is virtually every increase in the number of competitors in the market resulted in a decrease in prices. The most notable decrease in price came when the second generic entered into the market.

You say, "Well, why is this the case?" Let's say that there is, again, just one producer, a monopoly producer, and they raise the price. What is the consumer to do? If it's a case of—like the EpiPen, where someone has got to have the epinephrine—it's a life or death situation—you're left with little recourse.

You introduce one competitor, and all of a sudden, if the price goes up for one, that competitor has a choice, and they can do one of two things. They can either not raise their price and increase their market share and increase their profitability, or, given that explicit occlusion is illegal, they could still engage in something called price following and start raising their price anyway.

When there are smaller numbers of producers in any market, this price following is more common. Again, what the FDA found was that it took as little as that third company, the second generic, to virtually wipe away this price following effect and drive prices down in a market.

The key question, then, is not whether more competition is good or bad. It's a fairly straightforward microeconomic principle that more competition will lead to lower prices for consumers. The question is where would these barriers to competition arise? Why are we finding in some markets an absence of competitors?

We can think about this broadly first. We can think about circumstances that cause a reduction in competition. They might include things like control over scarce inputs. Think about De Beers and control over costume grade diamonds. They've got the diamonds. No one else has the diamonds, so they might be able to have some extra market power.

We can think of IBM at the birth of super computers and thinking they had some technological superiority. They knew something that other people didn't know. That could give you some advantage. We could think about really high up front costs. There are not a lot of jumbo jet producers in the world. There's Boeing, there's Airbus. There's two, and why might that be the case? You'd have to

have a company larger than most countries' GDP to even startup a company.

The other big one would be if there's economies of scale in production. Think of electricity production. Small scale production wouldn't be cost efficient.

Finally, the last major barrier to competition comes from government regulations itself. The Senator alluded to some of these in his opening statement. They include patents, licensing rules, and government prohibition on competition. Think in this case of the post office. There's an actual prohibition against competing in the delivery of mail.

When we look at the pharmaceutical industry, generally, and the EpiPen situation, specifically, what we don't see are these big startup costs. Sure, there are some startup costs. We're not talking Boeing-sized startup costs. Epinephrine has been around for a long time. There's no big scientific reasons, no great technology that's not available to other people.

We can go one at a time and go through most of the reasons why there is this barrier to competition. It turns out the barrier does exist, but it's coming specifically from that last item, the government regulations.

First of all, there's the patent situation. Again, there's a reason. Society faces a tradeoff. We can offer patents, which gain a company monopoly status, and we know that by giving them monopoly status, that's going to increase their pricing power. We do it on purpose, and the reason society has decided to do this on purpose is to encourage innovation. If you can't recoup your research and development costs, people will not spend time and money to expand the technological frontier and improve people's lives.

The question is not whether we have patents or not. The question is the optimal length of patents. One of the big issues we're facing now in the pharmaceutical industry are patent extensions. Sure, you came up with a great idea at the beginning, but now maybe instead of taking the pill once a day, you can take it twice a week, and is that worthy of patent protection. What we need to do is look at a tradeoff between the value of innovating to a twice-a-week pill or a different delivery mechanism for the epinephrine versus the extra consumer surplus we could generate by extending competition more quickly.

The second area, then, is going to be with licenses. In this case, we're thinking FDA approval itself. You have to obtain FDA approval to become a competitor. So when we look at absence of competition in the market, particularly in the face of high prices, you say, "Well, why aren't there new competitors just jumping in?" Again, if there are not huge technical barriers, what's going on? It turns out there is a very lengthy, as you noted, process for approval to be a competitor.

If we're thinking shoes, if we're thinking a shoe store, and the only shoe store in town jacks up the price of shoes, there's a very low barrier to start a new shoe store and compete, or you could have online competition. Here, though, if you had to ask "Mother, may I?" from the government, and the government says, "Three years from now, 4 years from now, 7 years from now, you might be able to, if you fill out enough paperwork, pay enough, between

$1 million and $5 million in application costs to start a shoe store," you could see how there could be a lot of shoe stores that have a lot of monopoly status. You would artificially be restricting the number of competitors to the market.

If we're doing this on a logical basis, should the FDA have licensing? You can make a good argument for that, that they want to ensure product safety, and, again, we're going to face a tradeoff. Product safety is going to be the biggest issue here. The question is not do we have any approval process, but is 4 years, 5 years, 7 years the appropriate amount, particularly in cases where we already know what the drug does. It's not a new drug. There aren't new side effects. It's the same drug in a generic form.

Does there need to be some product testing to make sure that the drug is what it says? Sure. Does that need to take 5, 6, 7 years? Certainly, by increasing these—the FDA increasing the cost of getting generics to the market has done a huge disservice to consumer surplus. At a minimum, they should do a cost-benefit analysis and determine in each case—is this going to be the first generic, or is this going to be the 17th generic? We know from the evidence that the 17th generic does not reduce prices as much in the market as the second or, most notably, the third competitor overall with the second generic. If the FDA is facing scarce resources, like we all do, we could hope that they could prioritize to those areas in terms of approving new drugs that will, in fact, lead to the highest increase in consumer surplus.

The last barrier to competition and corresponding policy change is when the government itself regulates the use of an item. In this case, with EpiPen, there were some States and local school districts that mandated specifically that it was EpiPen that had to be stored at the school and the competitor was not allowed. When that's the case, you restrict entry into the market. You're not even allowing the competitor to come in and bid down price.

Restricting government's ability itself to pick winners and losers, to say, "You must choose this drug versus that drug," will stand to increase competition and consumer surplus.

Thank you.

[The prepared statement of Mr. Strow follows:]

PREPARED STATEMENT OF BRIAN K. STROW, PH.D.

My name is Brian Strow, Ph.D., WKU BB&T Professor for the Study of Capitalism and Professor of Economics at Western Kentucky University. I am grateful for the opportunity to come before the U.S. Senate Committee on Health, Education, Labor, and Pensions' Subcommittee on Children and Families to testify regarding the benefits to consumers of increased competition by producers, provide evidence of the value to consumers of increased producer competition in the pharmaceutical industry, explain how barriers to producer competition arise in markets generally and the pharmaceutical industry specifically, and offer policy suggestions aimed at reducing said barriers for the benefits of consumers.

THE BENEFIT TO CONSUMERS OF COMPETITION

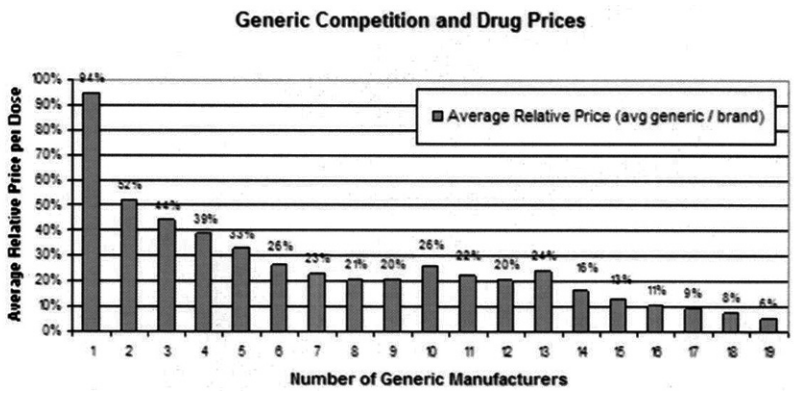
For consumers, choices are "good." More choices are "better." Economists measure "good" and "better" in terms of consumer surplus. Consumer surplus is the difference between the amount of money that consumers are willing and able to pay for a good or service and the price they actually have to pay for the good or service. If one is willing and able to pay up to $10 per for one dose of a prescription drug and the price is set at $10, there is no consumer surplus. If the price of the prescrip-

tion drug falls to $4, then the consumer gains $6 of consumer surplus when they purchase the drug.

Competition among producers in markets for goods or services works to lower prices and improve quality in said markets thereby increasing consumer surplus. In order to maximize profits, monopolists will tend to artificially restrict the quantity of a good or service available on the market and increase the price of the good or service. As each new subsequent producer enters the market, consumers gain greater decisionmaking power over what good or service to purchase. Any given producer loses power over the consumer and must compete for said consumer's business by offering a better good or service or lowering the price they charge. Standard microeconomic theory suggests that as the number of competing producers increases, prices fall.

THE BENEFIT TO CONSUMERS OF PHARMACEUTICAL COMPETITION

In 2005, the U.S. Food and Drug Administration reported a direct relationship between the number of drug producers in a market and the average price of the drug for sale that occurred between 1999 and 2004. Their chart is included below. While increased producer competition was found to generally lower average drug prices, the best news for consumers was that the largest percentage benefit from increased competition occurred when merely the second generic drug entered the market. Reductions in drug prices directly related to increased producer competition are the rule, rather than the exception, in the pharmaceutical industry.



Source: FDA analysis of retail sales data from IMS Health, IMS National Sales Perspective (TM), 1999–2004, extracted February 2005.

WHY BARRIERS TO COMPETITION ARISE

In general, barriers to producer competition arise from a limited set of circumstances. These circumstances include control over scarce inputs (De Beers' control over costume grade diamonds), technological superiority (IBM at the beginning of super computers), large up-front costs (the jumbo jet industry), the presence of economies of scale (large scale electricity production may be cheaper than small scale production), and government regulations (patents, licensing rules, or government prohibition as in the case of the postal monopoly).

In the absence of these barriers, if a company were to dramatically increase the price of their good or service in absence of an increase in their production costs, one of two things will occur. Their competitors will not respond to the price increase and gain market share or they will respond by increasing their own prices (explicit price collusion is illegal). The larger the number of competitors, the greater the likelihood that one producer will attempt to gain market share and not raise prices. As they lose market share, the other producers are forced to reduce their prices or get squeezed out of the market.

If there are a small number of competitors and they all increase their prices, the increased price acts as a signal to potential producers indicating that resources need to be reallocated into the increased production of the very good or service whose price has been increased. As long as the price of the good or service remains above the price that would be derived from perfect competition, the signal for new entrants remains. New entrants will enter into the market until the price returns to the price suggested by a perfectly competitive market. (F.A. Hayek, *The Use of*

Knowledge in Society 1945 and Milton Friedman, *Capitalism and Freedom*, Chapter 8).

As in the recent case of EpiPen price increases, one must address the question of what specific barriers to competition exist in the short run and the long run. If no barriers to entry existed for producers, they would have instantaneously responded to higher EpiPen prices with similar products aimed at the same consumers.

EpiPen producers don't have access to scarce resources or superior technology. Other drug makers also have the ability to engage in large scale drug production, so the argument that new production lines take time to implement only carries short term explanatory power. That is, a drug maker could only increase prices for a specific drug for a short period of time. Dramatically increasing their prices risks long term damage to the drug maker's public image which risks their relationship with consumers in other product markets.

The chief barrier to competition in the pharmaceutical industry is government regulation—in many forms. Patents, issued by the United States Patent and Trademark Office offer producers limited term monopoly rights to the production of a good. The U.S. government purposefully restricts short term producer competition in order to incentivize long run innovation. If we were to the point where we had invented all there was public benefit to invent, disbanding the patent system would increase competition and consumer surplus. We do not yet live in such a world, and reducing the economic returns to patents risks diminished research and development in the pharmaceutical industry.

The FDA has to approve or license the production and sale of pharmaceutical drugs in the United States. The longer time (and financial burden) it takes to gain FDA approval for drug production to commence, the less competition pharmaceutical producers face in the short run which gives them increased pricing power thereby reducing consumer surplus.

Last, government monopolistic regulations themselves can contribute to the lack of competition. In the case of EpiPen, many State and local governments mandated that schools stock epinephrine. Some of these governments entered into agreements with Mylan (the producer of EpiPen) that they not buy from EpiPen's competitors.

POLICIES DESIGNED TO LOWER BARRIERS TO COMPETITION IN THE PHARMACEUTICAL INDUSTRY

As there are three specific factors that reduce long run competition in the pharmaceutical industry, reforms proposed to successfully increase competition in the pharmaceutical industry must specifically address one of these three factors: patent law, the FDA regulatory process, and direct government involvement in drug markets.

Patent reforms could include increasing the innovation bar necessary to qualify for patent protection. Is changing a pill from a daily pill to a twice a week pill really worthy of a patent extension if it decreases consumer surplus? At a minimum, the patent office should be required to do a cost benefit analysis before granting patent extensions.

Increase the speed at which generic drugs are approved by the FDA. While the approval process for generics is shorter than for new drugs, the FDA could be incentivized to use their scarce resources in ways that maximize consumer surplus. The FDA could be required to do a cost benefit analysis regarding their usage of scarce inputs. This would work to expedite the very drugs whose benefit to consumer surplus are the greatest.

Don't allow agents of the public sector to pick which specific producer gains monopoly access to a public market. Analysis by Best Practices LLC. Indicates that the most effective ways for drug makers to increase profits are through patent extension and large volume purchaser contracts. By eliminating public officials' ability to engage in exclusive drug deals, one can ensure increased competition in the pharmaceutical industry.

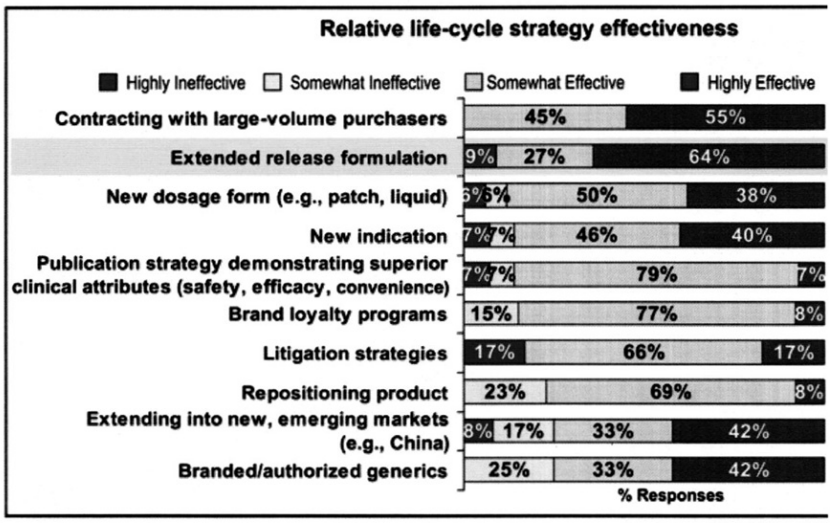


Fig. 1. Extended-release formulation is rated as one of the most effective methods of extending the life cycle of a drug. Credit: Best Practices LLC

To summarize: competition is good more competition is better, the chief barrier to increased competition in the pharmaceutical industry is government, policies designed to lower drug costs and increase consumer surplus need to begin with regulatory reform.

Senator PAUL. Thank you. Our next witness is Dr. Scott Gottlieb. He is a Resident Fellow at the American Enterprise Institute, a well-known writer, and a practicing physician.

Scott.

STATEMENT OF SCOTT GOTTLIEB, M.D., RESIDENT FELLOW, AMERICAN ENTERPRISE INSTITUTE, WASHINGTON, DC

Dr. GOTTLIEB. A reformed government bureaucrat, having worked at FDA for a number of years.

I want to thank you for having me today, Senator, and for the opportunity to testify before the committee.

I want to pick up on some of the discussion around the regulatory failure and around the lack of competition. The lack of competition in this market and for the EpiPen product does stem from regulatory failure stemming from FDA policy, and I think that policy can be fixed.

The first breakdown, in my view, is just the sort of growing cost and complexity of that FDA approval process. To give you some statistics on that, for generic drugs that were launched in 2015, it took about 4 years for them to be approved, to go through the FDA process, largely because less than 1 percent of the applications actually get reviewed and approved on their first cycles. You have multiple cycling of these generic applications, and often it's over minor issues that don't get to the overall safety and effectiveness of the products.

At the same time that the complexity has gone up, so has the cost. When I was at FDA, we used to, as a rule of thumb, say that

a generic drug application—to file and get it through FDA would cost about a million dollars, and a category of drugs would have to reach about $10 million in total revenue to be genericized, to have sufficient revenue to make it worth filing that million-dollar application.

Today, it can cost upwards of $20 million to file a generic drug application, and the general market rule of thumb is that a drug would have to fetch between $25 million to $50 million in revenue to justify the investment. So you have a situation where you have these low utilization products on the market that don't have any competition.

Of about 1,300 branded drugs on the market, 10 percent have lost all patent protection and only have one competitor. These are some of the high priced drugs that we have been talking about in the news, drugs like clomipramine, which had an 1,800 percent price hike from 2013 to 2014; fluconazole, a 996 percent increase over the same year; doxazosin, a 1,169 percent increase. You have one competitor on the market. They have to amortize the cost of developing that product over a very low volume. There's no competitors coming in trying to drive the price down, and you end up having these big price increases.

These problems are compounded when it comes to the class of generics that I would call complex generics or complex drugs. Typically, a complex drug is a drug that has something unusual about its formulation or its mechanism of action that makes it hard to determine that it's the same exact drug as the drug it's trying to copy based on a traditional test that we require as part of the generic drug process.

The generic drug process requires what are called bio-equivalents and bio-availability studies, which basically means that if you take the drug and you can measure the drug in someone's blood at the same level and in the same proportion as the drug it's trying to copy, you can get approval just on the basis of those tests, just by showing that your drug gets into the blood the same way and stays in the blood for the same length of time. That was built for a world when drugs were fairly simple chemicals. They were all pills. They were small molecules.

In a world where drugs are complex and just merely measuring them in the blood isn't a good approximation of what their benefit might be, it's a lot harder to put those drugs through the traditional generic drug process. Think, for example, of a drug that acts locally like a metered dose inhaler for asthma. It's acting directly on the lungs, so measuring how much of that drug gets into the blood isn't going to be a good approximation for how it works in the lungs. In fact, it is the case that we don't have generic competition to some very expensive metered dose inhalers for asthma that have long lost patent protection.

Or think of a topical agent like a dermatological cream. If you want to know why old acyclovir costs so much, it's because it's hard to develop a generic formulation of something that acts locally and topically.

In the case of EpiPen, it too would fall into this category of complex generics, and the complexity here is the device. It's the product for delivering the drug, the auto injector. The problem is that

if someone wants to copy EpiPen, the law says that they have to have the exact same instructions for use in their label as EpiPen. In fact, Mylan has patented some of the unique attributes of their auto injector that deal with how you would instruct a patient to use it. If someone wants to copy EpiPen, they basically have to copy EpiPen's instructions for use, but the instructions for use deal with patented aspects of the auto injector.

There's a catch–22 here. If someone wants to develop a different auto injector, a different form of epinephrine, a different device, and wants to get approval as a new drug, because they can't go through the generic drug process because they can't copy EpiPen's label, FDA might say to them, "Actually, we don't think you can be a new drug because you're basically the same ingredient as EpiPen so you have to go through the generic drug process." You can get caught in a catch–22 of sorts, and I think that there are companies caught in this process if you were to ask FDA.

What's the up-shot here? The generic drug law is a very old law that was written at a time when drugs were very different and were basically simple chemicals. Now that we have these categories of complex generics, we might think about changing the law to allow FDA to have more discretion to ask for different complements of information for the purposes of developing generic copies of some of these drugs.

In the case of EpiPen, that might mean allowing a generic copy to EpiPen to have slightly different instructions for use, as long as it's not going to create a patient safety issue, but still be considered a generic formulation of EpiPen and still be substitutable at the point of the pharmacy to provide that kind of price competition that we seek in the market.

With that, I'd be happy to answer questions. I appreciate being here.

[The prepared statement of Dr. Gottlieb follows:]

PREPARED STATEMENT OF SCOTT GOTTLIEB, M.D.[1]

Mr. Chairman, thank you for the opportunity to testify before the committee.

The rising list price of drugs such as the lifesaving EpiPen autoinjector,[2] coupled to the increasing exposure that consumers have to these costs as a consequence of secular change in the design of insurance coverage, has appropriately focused increasing scrutiny on how drugs are priced. It's often argued that drugs are one of the last vestiges of market-based pricing in our highly regulated health care industry. By contrast, regulators in Washington set most prices for clinical services. It's true that drug makers have more pricing discretion than other sectors in health care, whether it's in comparison to hospitals, providers, or even medical device makers. The market for drug products is hardly a utopia of free market pricing and vibrant competition. The drug market is subject to its own peculiar price setting and regulation. These rules undermine the competitive opportunities that could help inspire more choice and competition, and help lower costs.

Today I want to talk about three areas where I believe that regulation creates barriers to pharmaceutical competition. I will focus my remarks on how policymakers could remedy these market failures, enable more choice, and stimulate more price competition.

The first issue deals with the way that the Food and Drug Administration (FDA) regulates drugs. Here I focus on what I categorize as complex medicines. These are

[1] The American Enterprise Institute for Public Policy Research (AEI) is a nonpartisan, nonprofit, 501(c)(3) educational organization and does not take institutional positions on any issues. The views expressed in this testimony are those of the author.

[2] EpiPen, "Prescribing Information," August 2012, *https://www.epipen.com/hcp/-/media/files/epipen/prescribingpercent20information.pdf.*

circumstances where the drugs have certain intricacy associated with their formulation or delivery. Developing cheaper, copy versions of these complex drugs, after legitimate patents have lapsed, are made especially difficult by shortcomings in regulatory policy.

The second area relates to existing price controls and mandatory rebates in programs such as Medicaid and 340B. These government rebate schemes put upward pressure on drug prices, by creating financial pressure to raise the list prices on drugs in order to provide fiscal room for accommodating the mandatory kickbacks. The problems associated with this system are longstanding and manifold. But these burdens are made more acute by a recent, sharp, and secular change in the structure of drug insurance coverage that has left more consumers exposed to the list price of drugs, before the rebates are applied.

Consumers who increasingly find themselves underinsured for drugs—even while more medical care shifts toward the use of higher-cost, specialty medicines—are not directly benefiting from the rebates that end up lowering the real, net price of the medicine. The health plan benefits from these rebates. They help offset premium costs. But the underinsured consumer can end up paying the full list price, not the post-rebate price.

In the case of EpiPen, a drug product that's used for the emergency treatment of certain allergic reactions, the invoice price for a two-pack EpiPen product in 2016 is currently about $600. But these invoice or "list" prices do not account for any rebates and other discounts. According to recently published data, the net price received by Mylan for each EpiPen 2-Pak was $274.[3] This is the "net" or "real" price.

The remaining 54 percent of the list price was split among Pharmacy Benefit Managers (PBMs), insurers, wholesalers, and pharmacy retailers.

Toward addressing these challenges, our drug market would be more competitive if drug makers were able to offer—and purchasers able to demand—up-front discounts off the list price of drugs, rather than have to settle for back-ended rebates that aren't available to consumers when they purchase a drug at the pharmacy counter. But legal precedents that Congress could address through legislation largely stand in the way of the ability of drug purchasers to demand discounts, and the feasibility of drug makers to offer them.

Third and finally, there are obstacles to the more competitive pricing of the sort of "single source" breakthrough medicines that are providing some of the most meaningful public health advances. These include branded drugs that provide substantial benefit and even outright cures for some forms of cancer and diseases such as Hepatitis C.

We need to allow innovative drugs that offer meaningful advances in medical care to be priced in a market system based on the benefit that they offer, and the cost of the capital required to underwrite the long and uncertain development path for creating these sorts of breakthroughs. We don't want to undermine the model for investment and innovation that makes these advances possible and has given us the most vibrant market for the research and development of biotech and drug products in the world.

At the same time, those who purchase these drugs should be able to demand prices that relate to the benefits that these products deliver and the circumstances for which they are prescribed. Right now, government rules regrettably prevent this sort of price discrimination based on indication and outcomes. Drug makers can't offer prices based on measures of benefit or grounded in the purpose for which a drug is prescribed. Patients can't demand these sorts of price concessions.

FDA REGULATION SHORTCOMINGS OBSTRUCT COPIES OF COMPLEX GENERICS

Drugs such as EpiPen fall into a category of products that one might classify as complex generic medicines. It's been noted that the active ingredient in the EpiPen is epinephrine, a very old drug. What makes the EpiPen unique is its delivery vehicle—an autoinjector that's packaged in a convenient, pen-like device. The product's key attribute is its ability to reliably deliver accurate doses of the essential medicine. This meaningful convenience and the product's reliability allowed EpiPen to capture a substantial portion of the market for injected epinephrine, but it is not the only such product available.

The current market for these epinephrine products breaks down this way: Of the 4.2 million prescriptions for epinephrine products written in 2016, about 3.9 million were for combination products (i.e., autoinjectable devices containing the medicine,

[3] Mary Caffrey, "How Increased Cost Sharing Triggered the EpiPen Crisis," AJMC.com, August 24, 2016, *http://www.ajmc.com/focus-of-the-week/0816/how-increased-cost-sharing-triggered-the-epipen-crisis.*

such as the EpiPen). According to IMS Health, Mylan represented about 3.8 million of these prescriptions. Impact Laboratories comprises the bulk of the remaining market share of autoinjectables. A third autoinjectable combination product, Auvi-Q marketed by Sanofi, was voluntarily recalled in 2015 due to malfunctions with the device.[4]

In addition to these autoinjectable products, a number of generic forms of epinephrine are available in ampule and vial form as well as packaged in a prefilled syringe. These products constitute a small number of prescriptions written for epinephrine in 2016. The top four vial manufacturers totaled about 217,000 prescriptions.

While the EpiPen's manufacturer, Mylan, maintains some important intellectual property around its autoinjector that the company believes differentiates its device, this should not—and has not—prevented other companies from developing their own pen-like devices for autoinjecting epinephrine. However, the way that FDA administers its generic drug regulatory process has left the agency tied in some policy knots when approving similar products as generic substitutes for EpiPen. At the same time, other regulations make it hard for competitors to EpiPen to get their products approved as new, branded alternatives to EpiPen through the new drug approval pathway. Policy shortcomings can leave potential competitors in a regulatory Catch–22.

One issue relates to the existing statute and FDA regulations that govern the approval of generic drugs, the Abbreviated New Drug Application (ANDA) process. FDA maintains that, if a patient has to be retrained to use a generic alternative to a branded product, then the alternative product cannot bear the same labeling as the drug it seeks to copy, and it cannot meet the burden of the ANDA process and be approved as a generic equivalent. The copy drug can't be considered the "same" and serve as a substitutable alternative.

This means that an alternative to a complex drug or a complex drug and device combination such as EpiPen would have to function in the exact same manner as EpiPen. To the extent that Mylan maintains some intellectual property around some of the functions of the EpiPen that correlate to some unique instructions on how to use the device, this can impede entry of generic competitors to EpiPen—even if most of the fundamental intellectual property (IP) on the drug and the device has lapsed.

At the same time, under FDA's existing rules it could be difficult for a competitor to EpiPen to seek approval under the longer and costlier new drug approval process as a branded alternative to EpiPen. Here is the Catch–22, of sorts, at play. A competitor might not be able to go through the ANDA route, but may not qualify as a new drug, either.

This could occur in an instance where a competitor to EpiPen might be filing for approval under a regulatory pathway referred to as 505B(2). The regulatory pathway is named for the section of FDA's statute that gives rise to this alternative approval process.

First, it would be unusual for FDA to approve a drug through the 505B(2) pathway and allow it to be therapeutically substitutable for another product (in this case EpiPen). So any EpiPen alternative approved under 505B(2) would not be a true generic alternative to EpiPen. Such an approval would, nonetheless, still create market competition that could help lower costs. But there is a second regulatory obstacle. In situations where a product is likely to be a therapeutic equivalent to a drug, FDA encourages (and could in some cases require) a drug developer to file as an ANDA. So there could be situations where FDA compels drug makers to file under the ANDA route, only to hit a policy obstacle in trying to copy the instructions for use in the EpiPen label without infringing some of EpiPen's IP around its autoinjector and its unique functions.

Such is the case with another epinephrine product, Adrenaclick.[5] Like EpiPen, it is a formulation of epinephrine delivered through an autopen. Pharmacists cannot substitute it for EpiPen, despite the similarities. That's because while it's the same drug, Adrenaclick has a different autoinjector and, thus, bears a different set of instructions for using the device. It cannot be approved as a generic product that is substitutable for EpiPen.

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[4] U.S. Food and Drug Administration, "Sanofi US Issues Voluntary nationwide Recall of All Auvi-Q® Due to Potential Inaccurate Dosage Delivery," October 13, 2015, *http://www.fda.gov/Safety/Recalls/ucm469980.htm.*

[5] The Adrenaclick sells for a list price of around $140 per unit.

These issues fall broadly into a category of challenges that relate to the approval of "complex generic drugs."[6] While there is no official definition of "complex" generics, one can broadly define complex generics as generic drugs for which it is particularly difficult to establish therapeutic equivalence as defined in the Orange Book.

Some complex generics present significant challenges in establishing pharmaceutical equivalence due to problems related to physiochemical characterization. For some, a simple bioequivalence study is not enough to establish that the generic drug will have the same clinical and safety profile as the reference-listed drug that it seeks to copy.[7]

In soliciting a study from the Government Accountability Office, Congress defined complex generics as drugs that were not fully characterized because the active pharmaceutical ingredient has molecular diversity, because scientific analytic methodologies are unable to fully identify the molecular structures and physiochemical properties of the active ingredient, and because the nature of the active ingredient is not understood well enough to identify the drug's mechanism of action that produces its therapeutic effect.[8]

Similarly, complex drugs have also been defined by authors as nonbiological products "where the active substance is not a homo-molecular structure, but consists of different (closely related and often nano-particulate) structures that cannot be isolated and fully quantitated, characterized and/or described by state-of-the-art physicochemical analytical means and where the clinical meaning of the differences is not known."[9] In this regard, complex drugs can share characteristics with biologicals.

FDA has defined complex generics more broadly to include these circumstances, as well as situations such as EpiPen, where the complexity is related to the drug's delivery. This could include situations like EpiPen, where a drug is delivered through a complex device.

This might involve, for example, a drug that acts locally on tissue lining the gut (such as oral vancomycin) or an inhaled drug that acts directly on the lungs (like metered dose inhalers (MDIs) for the treatment of asthma and other lung diseases). Complex drugs might also be one that is delivered through a complicated delivery mechanism such as EpiPen or, to take another example, a drug delivered through a controlled-release patch.

FDA has faced perpetual policy challenges, in part of its own making, when it has tried to "genericize" a growing number of these complex drugs through its ANDA pathway. Because of the FDA's policy constraints, as well as its own scientific ambiguity when advancing regulatory principles for developing copies of complex drugs, sponsors often say that they feel like they are "shooting in the dark" when developing the product, preparing dossier for an effective FDA filing, or engaging in the back-and-forth between FDA and the company during the review.

For example, the agency delayed for years the approval of a generic alternative to long-acting heparin—long after the legitimate intellectual property on that medicine had lapsed.[10] Similar delays challenged the approval of complex generic formulations, such as oral vancomycin, liposomal Doxorubicin HCl injection,[11] and topical Acyclovir ointment.

In other cases, FDA made errors in how it approved generic alternatives to complex drugs like IV iron, requiring its decisions to be revisited. Or FDA established regulatory principles that were widely criticized and ultimately rescinded, such as when FDA tried to address the generic approval of certain eye drops that act topi-

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[6] Robert Lionberger. "Complex Generic Drugs," presentation at the Generic Pharmaceutical Association Fall Technical Meeting, October 29, 2013, *http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM374191.pdf.*

[7] Aloka Srinivasan, "Complex Generics: Maximizing FDA Approval Prospects" Parexel, 2015, *https://www.parexel.com/files/6714/3076/9385/ComplexGenerics_WPApril2015_final.pdf.*

[8] Zachary Brennan, "House Panel Calls on GAO to Study FDA's Approval Pathway for Complex Generics," Regulatory Affairs Professionals Society, December 15, 2015, *http://www.raps.org/Regulatory-Focus/News/2015/12/15/23775/House-Panel-Calls-on-GAO-to-Study-FDApercentE2percent80percent99s-Approval-Pathway-for-Complex-Generics/.*

[9] Huub Schellekens et al., "How to Regulate Nonbiological Complex Drugs (NBCD) and Their Follow-On Versions: Points to Consider," *AAPS Journal* 16, no. 1 (January 2014): 15–21, *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3889532/.*

[10] Alicia Mundy, "FDA Approves Generic Lovenox," *Wall Street Journal*, July 24, 2010, *http://www.wsj.com/articles/SB10001424052748703294904575385133623904548.*

[11] Rao N.V.S. Mamidi et al., "Pharmacokinetics, Efficacy and Toxicity of Different Pegylated Liposomal Doxorubicin Formulations in Preclinical Models: Is a Conventional Bioequivalence Approach Sufficient to Ensure Therapeutic Equivalence of Pegylated Liposomal Doxorubicin Products?" *Cancer Chemotherapy and Pharmacology* 66, no. 6 (November 2010):1173–84, *https://www.ncbi.nlm.nih.gov/pubmed/20661737.*

cally on the eye. In the latter case, for products that act locally on tissue rather than acting systemically after being absorbed into the blood, FDA can lack reliable, rigorous principles for demonstrating sameness in how two versions of a drug act on the target organ.

The problem is that the generic drug approval process was crafted at a time when most drugs were relatively simple, small molecule pills. The process for copying these drugs was relatively straightforward. The system for proving sameness largely turned on the ability to show that a copy of a drug can get into the blood at the same levels and in the same timeframe as the branded drug that it was seeking to emulate. It could then be postulated, based on these "bioequivalence" and "bioavailability" studies, that the generic drug would have the same therapeutic profile as the branded drug that it sought to copy.

This classical generic pathway was sufficient for many well-defined, small, low molecular weight drugs where the analytical testing fully characterized the product and showed pharmaceutical sameness to the reference-listed drug. Together with a proof of bioequivalence to the reference product, this information allowed for the submission of an abbreviated file (ANDA) with a waiver for efficacy and safety studies. FDA would nonetheless be able to declare that the copy was fully substitutable for the reference drug.

With complex generics, the ability to determine sameness based on bioequivalence and bioavailability is sometimes not as straightforward. That might be because the complex drugs act locally on an organ and therefore, the level of drug found in the blood is not an effective surrogate for surmising its therapeutic effect. Or the complex drug might be an intricate formulation, where the concentration of active ingredient found in the blood cannot be accurately measured. Or the drug might be like the EpiPen and involve a complex delivery system that requires instructions for use that cannot be precisely copied in labeling from one version of the product to the next.

As a consequence, I believe that Congress should consider legislation to modernize the generic drug framework to allow FDA greater discretion in the kinds of data it relies on for its generic approvals in this narrow category of complex drugs. This would require, for example, granting FDA the ability to ask for more than just bioequivalence and bioavailability data in making judgments around sameness. Or it might require Congress to grant FDA more discretion to make minor modifications in generic labeling to account for small variations between a branded drug and the proposed generic copy, for example, when instructions for use might be marginally different.

It's noteworthy that generic industry stakeholders named the creation of a specialized review pathway for complex abbreviated new drug applications as a priority during user fee negotiations. The agency has also discussed with generic drug manufacturers the need for more clarity from FDA in this pre-ANDA space, according to meeting minutes.

These challenges with the complex drugs are compounded by the overall slowness and inefficiency of the generic drug approval process. As I recently noted in *The Wall Street Journal*,[12] the complexity and cost of completing even an average (less complex) generic drug application has also grown enormously. In 2003, when I began working at the FDA, we estimated that it cost less than $1 million for a firm to file a generic drug application. A drug would have to earn about $10 million in annual revenue before it would be subject to generic competition. Today, filing a generic application requires an average of about $5 million and can cost as much as $15 million. This means that a drug may not face brisk generic competition until it exceeds $25 million in annual revenue.

As I previously noted, the key to the generic economic model is to keep entry prices low enough to attract multiple competitors. One study estimated the cost to consumers of generics to be 90 percent of the branded drug's price if there is only one generic entrant. But the price falls to 63 percent if there are five competitors and 40 percent when there are 10 competitors. Yet of the 1,328 branded drugs on the market, about 10 percent have seen patents and exclusivities expire, but face no generic competition.[13]

Some of these are the high-cost medicines that are the subject of political wrangling, drugs such as clomipramine (which saw a 1,818 percent price hike from 2013

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[12] Scott Gottlieb, "How Obama's FDA Keeps Generic Drugs off the Market," *Wall Street Journal*, August 19, 2016, *http://www.wsj.com/articles/how-obamas-fda-keeps-generic-drugs-off-the-market-1471645550.*

[13] U.S. Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation, "Understanding Recent Trends in Generic Drug Prices," January 27, 2016, *https://aspe.hhs.gov/pdf-report/understanding-recent-trends-generic-drug-prices.*

to 2014); fluconazole (996 percent increase); and doxazosin (1,169 percent). Each of these drugs accounts for less than $2 million in total Medicaid spending, meaning that very few people are using them. Given the high generic entry costs and the infrequent use of these drugs, it's often no longer economically viable for more than one firm to make them.

Owing to these economic challenges, infrequently used generics may now have only one competitor and cost as much as branded drugs. When the price of a drug rises, it becomes profitable and the target of new competition. The FDA recently committed to review new generic drug applications in a 15-month cycle, an improvement over a median of more than 2 years for applications submitted in 2013.[14] For generics filed in 2009, the median review time exceeds 3 years. Yet generics launched in 2015 took about 4 years for the FDA to approve, since less than 2 percent of applications were approved on their first submission.[15] FDA committed to improve first-cycle approvals, but it still rejects most applications before demanding resubmissions, delaying competition.[16]

Toward addressing these challenges, in addition to defining a new path for complex generic drugs, FDA should also prioritize files for these sorts of busted generic drug categories, especially where the generic targets an uncommon and serious ailment. Companies that pursue copies of these "discarded" generics could receive a voucher that would allow them to get expedited review of another generic drug. The value of this voucher would give firms more incentive to market copies of low volume generics.

FDA must also scrap a draft rule it crafted to deliberately expose generic companies to rampant product liability suits—the so-called generic drug labeling rule.[17] FDA also needs to tailor its oversight of manufacturing to the way that generics operate, usually by manufacturing dozens of different drugs on each production line and hundreds of different medicines in a single plant. Right now, FDA is trying to force generics into the much costlier way that branded firms operate their manufacturing plants, by requiring that generic product lines be dedicated to just one or two different drug products.

The regulatory delays are even more apparent with the complex drugs. Yet these complex medicines comprise a growing and important portion of our therapeutic armamentarium. The generic entry of some important copies of these medicines, once the legitimate intellectual property has lapsed on the branded alternatives, has sometimes been needlessly delayed. This saddles consumers with unnecessary costs that were never intended when the generic pathway was envisioned. These shortcomings largely stem from the absence of scientific tools for determining sameness in these settings, and the regulatory framework to efficiently approve these copies through FDA's ANDA pathway. Yet the agency insists on trying to force these drugs down the traditional generic drug approval process. It's time for Congress to define a more efficient pathway.

PRICE CONTROLS FORCE REBATES AT THE EXPENSE OF DISCOUNTS

In the cost of medicines, another challenge facing consumers is the growing gap between the list price of drugs and the actual, net price paid by those who purchase the medicines on their behalf. In many cases the average net price is much lower than the list price. In fact, the average net price for drugs actually rose at a 5-year low in 2015 and is rising in relative concert with overall health care inflation.[18]

But the list prices of drugs are rising much more sharply. The gap between these two prices—the list price and the real, net price actually paid by health plans—reflects rebates that drug makers eventually pay to health plans as a way to provide money off the sticker price of a medicine. This byzantine system is an unintended consequence of past policymaking. But its growing impact on consumers is unmistakable.

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[14] U.S. Food and Drug Administration, "FDA/GPhA: Quarterly Meeting on GDUFA," March 23, 2015, *http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM442070.pdf.*

[15] Janet Woodcock, "Implementation of the Generic Drug User Fee Amendments of 2012 (GDUFA)," testimony before the Committee on Health, Education, Labor, and Pensions, U.S. Senate, January 28, 2016, *http://www.help.senate.gov/imo/media/doc/Woodcock5.pdf.*

[16] Gottlieb. "How Obama's FDA Keeps Generic Drugs off the Market."

[17] Ed Silverman, "Generic Drug-Safety Rules Debated," *Wall Street Journal*, February 26, 2015, *http://www.wsj.com/articles/generic-drug-safety-rules-debated-1425009063.*

[18] Policy and Medicine, "IMS Releases 2016 Report on Prescription Drug Spending—Net Price Growth 2.8 percent in 2015," May 2, 2016, *http://www.policymed.com/2016/05/ims-releases-2016-report-on-prescription-drug-spending-net-price-growth-28-in-2015.html.*

As more consumers find themselves on health plans that have adopted very high deductibles, that also use closed and narrow drug formularies that leave a growing number of important medicines completely uncovered, and that use fixed coinsurance rather than fixed co-pays as a way to distribute costs to consumers, these conditions mean that the high list prices on drugs are the prices being paid by a growing number of consumers when they buy medicines at the pharmacy counter. Recent data from Kaiser that examined drug spending from 2004 to 2014 showed just how much these out-of-pocket costs have risen, far outpacing the costs paid by the health plans. Average payments toward deductibles more than tripled, rising 256 percent, and average payments toward coinsurance more than doubled, rising 107 percent. Over this time, average payments by health plans themselves increased only 58 percent.[19]

In the end, insurers may ultimately pay a price for a medicine that is half the "list" price paid up front by the consumer. The consumer never receives the direct benefit of the rebate, which gets paid to the insurer. This is precisely the circumstance that occurred for many consumers who purchased EpiPen at or near its list price.

These challenges are not just a function of high deductibles, which leave consumers exposed to the list cost of their drugs up to the point that they reach their deductibles. They are also a function of the growing use of narrow and closed drug formularies. These are schemes where insurers agree to cover to a shrinking list of drugs. When the drugs don't make it onto these narrow formulary lists, the closed structure of the formulary means that a drug is completely uncovered. Moreover, what consumers spend out of pocket doesn't count against their deductible or out of pocket maximums.

Now that these insurance features have become a mainstay of plans sold in the Affordable Care Act and are being sanctioned—if not encouraged—by Federal regulators as a way to accommodate the law's other regulatory costs, these same insurance designs are being imported into employer-sponsored coverage and coverage sold outside the exchanges. The Kaiser Family Foundation says that a quarter of workers with employer sponsored insurance (ESI) must pay the full cost of drugs before their coverage kicks in, up from 17 percent in 2011.[20]

The problem is that our current system provides incentives for companies to push lists prices higher, only to rebate the money later on the back end. Yet the rebates don't benefit consumers equally and they don't necessarily help offset the costs paid by those who need a particular drug. The rebates eventually make their way back to health plans to help offset the collective costs of premiums. But if a patient needs a particular drug, they will increasingly find that they are paying the full, negotiated price at the pharmacy counter. They never see the real "net" price, after the rebate is applied much later. The rebate is paid to the health plan, not the patient buying the drug.

Government policies help push the list prices higher, even as the net prices grow more slowly and in some cases even decline. For one thing, mandatory rebates required by programs such as Medicaid and 340B create incentives to launch drugs with high list prices if companies know they will be required to provide a fixed rebate off those charges. The use of average sales price in Medicare provides similar incentives to launch with a high list price, so do market conditions that largely prevent companies from offering up-front discounts to health plans and instead force them to compete based on providing rebates.

Because companies can negotiate based only on providing rebates rather than discounts, they know that the list price will bear increasingly less relation to their real price.[21]

This is another place where Congress can act to provide more market competition based on a system where purchasers can demand discounts up front, rather than back-ended rebates. Discounts would actually benefit consumers more evenly since consumers would have the opportunity to acquire drugs at the pharmacy at the discounted price.

It gets to the issue of why there is this artificial divide between the list and net price in the first place. Why, in other words, does the discounting in the drug space

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[19] Henry J. Kaiser Family Foundation, "2015 Employer Health Benefits Survey," September 22, 2015, *http://kff.org/health-costs/report/2015-employer-health-benefits-survey/view/exhibits/*.

[20] Robert Langreth, "Secret Rebates: Why Patients Pay $600 for Drugs That Cost $300," Bloomberg News, October 5, 2016, *http://www.bloomberg.com/news/articles/2016-10-05/patients-lose-out-on-big-pharma-s-secret-rebate-merry-go-round.*

[21] Scott Gottlieb, "Why Drug Makers Charge Outrageous Prices," CNBC, August 29, 2016, *http://www.cnbc.com/2016/08/29/why-drug-makers-charge-outrageous-prices-commentary.html*.

take the form of rebates paid to pharmacy benefit managers through a convoluted system on the back end of the transaction, rather than an up-front discount on the drugs?

It all stems from litigation in the late 1990s, brought by chain store pharmacies, that claimed that drug makers were colluding to discount to HMOs and not providing the same discounts to pharmacies, in violation of Sherman Antitrust Act. Drug makers contended that they did nothing wrong, and the discounts they made available to HMOs and providers were appropriate because these purchasers could move market share, while the pharmacies could not.[22] The litigation, which comprised dozens of separate cases, was ultimately consolidated into a single class action. Drug makers eventually settled the suits. They agreed to offer the same price to all channel partners. In other words, discounts that they made available to HMOs would also be available to pharmacies.[23]

To get around this outcome, the drug makers moved away from offering discounts and toward today's model of rebates. These rebates are based on complex formulas tied to some measure of units of a drug that are sold. The idea was that these rebates could be offered to everyone, including pharmacies. But the pharmacies would never be able to satisfy the burden of evidence to qualify for the rebates. Only the health plans could make the required representations related to how many units of a particular drug that it sold.

This raises an interesting question: Could Congress legislate to make it legal for drug makers to engage in price discrimination based on purchaser, offering discounts to one channel and not to another, so long as the drug makers were not conspiring to offer similar discounts? The answer, probably, is yes. If drug makers could offer discounts, purchasers would start demanding them. A discount would potentially be far more equitable, transparent, and pro-competitive than a rebate—especially where the rebate does not flow evenly to all consumers. Increasingly, it's consumers who are underinsured or uninsured that are stuck paying the full list price at the pharmacy counter.

If the "rebate" came in the form of up-front discounts, rather than back-ended givebacks, more consumers who are underinsured would benefit from the negotiated "real" price.

WE SHOULD ALLOW DRUGS TO BE PRICED BASED ON OUTCOMES AND INDICATIONS

Third and finally, we need to allow drugs to be priced based on how they are being prescribed and the outcomes that they deliver. Right now, regulation largely prevents the same medicine from being sold at different prices when it's being used in different settings. For example, a drug must largely be sold at the same price whether it is used in a high-value indication or used for which there might be less evidence of benefit. The same rules also largely prevent drugs from being priced based differently based on measuring the outcomes that they deliver to a group of patients. Regulations largely foreclose these kinds of arrangements, referred to collectively as value-based contracts.

Among other things, the Office of the Inspector General would probably view such indication-based discounts as an illegal inducement for doctors to prescribe more of a drug for a certain use. The FDA might interpret a contract tied to an indication or outcome that isn't precisely specified in the drug's FDA-approved label as a form of illegal, off-label promotion. In order to enable these arrangements, FDA would need to concede that commercial, contract-related communications constitute protected speech under the First Amendment and thus are not subject to the agency's active regulation.[24]

The way that the Medicaid best price and average sales price (ASP) are calculated (two price schedules that are maintained by the Centers for Medicare and Medicaid Services (CMS) for the purpose of price setting) would also present an obstacle to these kinds of value-based contracts. Under these price schedules, when drug companies offer indication- or outcomes-based discounts, they would be penalized across all of the indications for which a drug is prescribed. The discounts offered in one indication-based contract would lower the cost paid by every plan that ties its price to the ASP and Medicaid best price. It would also mean that the benefit of these discounts would be available to heath plans—through a lower overall Medicaid best

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[22] 21 Collin Levey, "Trial Lawyers Get Their Comeuppance," *Wall Street Journal*, July 19, 1999, *http://www.wsj.com/articles/SB932313148898376573.*

[23] Milt Freudenheim, "Drug Makers Settle Suit on Price Fixing," *New York Times*, February 10, 1996, *http://www.nytimes.com/1996/02/10/business/drug-makers-settle-suit-on-price-fixing.html.*

[24] Scott Gottlieb and Kavita Patel, "A Fair Plan For Fairer Drug Prices," Health Affairs Blog, July 11, 2016, *http://healthaffairs.org/blog/2016/07/11/a-fair-plan-for-fairer-drug-prices/*.

price and ASP—even when the health plans don't enter into the same value-based contracts.

Congress could act to provide a safe harbor when companies pursue these value-based contracts, to make sure that sponsors don't face regulatory obstacles from FDA, CMS, or OIG when the contracts meet certain public health goals. This could provide another vehicle for purchaser to demand more discounts from drug makers, and more ways to tie these discounts to circumstances and outcomes that matter most for patients.

CONCLUSION

These policies will take on increasing importance as the nature of drug coverage changes. These changes in coverage are partly a consequence of the Affordable Care Act, which favored narrow provider networks and drug formularies as a way to accommodate the cost of other regulatory priorities. This has left more consumers underinsured for their drug purchases. The exchange-based plans also relied on constructs like closed drug formularies. These same insurance constructs—having been rendered politically acceptable under the ACA—are being imported into commercial insurance plans as well. The National Business Group on Health, in a 2016 survey, found that 50 percent of employers reported that they plan to use a closed formulary to help control costs.[25]

The result is a sharp, secular change in the structure of drug coverage. More consumers are paying the list price for drugs, not the lower net price eventually paid by health plans, after rebates are applied. Congress can act to increase competition by enabling more drugs to reach the market, especially low-cost generic medicines. And enabling more health plans to negotiate discounts that can directly benefit consumers.

Senator PAUL. Thank you. We'll save the questions—we'll go around and save the questions.

Our next witness is Philip Almeter, who is the Senior Director of Pharmacy Acute Care Services and the 340B Programs at UK HealthCare here at the University of Kentucky.

STATEMENT OF PHILIP J. ALMETER, PharmD, SENIOR DIRECTOR, PHARMACY ACUTE CARE SERVICES AND 340B PROGRAMS, UK HEALTHCARE, UNIVERSITY OF KENTUCKY, LEXINGTON, KY

Mr. ALMETER. Thank you, Senator Paul, for the opportunity to provide testimony regarding the rising prices of medications in the United States. I am pleased to see that the HELP Committee has taken an interest in this issue.

The University of Kentucky's UK HealthCare operates two hospitals, several ambulatory clinics, and six retail pharmacies, one of which is a specialty pharmacy. In fiscal year 2016, we saw 38,000 discharges, 1.29 million outpatient visits, and UK Pharmacy Services dispensed 430,000 outpatient prescriptions.

Many of the medication price increases seen recently have affected UK and in my opinion can be classified into two basic groups: direct/obvious and indirect/less obvious. The direct/obvious reasons include increases in innovation, consequences of the FDA's Unapproved Marketed Drugs Initiative, changes in ownership, and the sole source effect. Indirect/less obvious reasons are surrounding the pharmacy benefit management impact.

The majority of the increases in innovation lies with the specialty pharmacy. In the last 5 years, spend with specialty medications has doubled, contributing to 70 percent of overall medication spend.

[25] Stephen Miller, "Employers Project Health Premium Hike of 6% in 2017," Society for Human Resource Management, August 10, 2016, *https://www.shrm.org/resourcesandtools/hr-topics/benefits/pages/health-premiums-2017.aspx.*

The primary drivers for this were therapy developments for hepatitis, autoimmune diseases, and oncology, which accounted for $19.3 billion in the increased spend. I believe 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.

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 into compliance with the approval provisions of the Federal Food, Drug, and Cosmetic Act, with one of the goals being to not adversely affect public health, imposing undue burden on consumers, or unnecessarily disrupting the market. My observations are that this new initiative incentivizes manufacturers to put forth R&D dollars for older agents in order to gain market exclusivity.

With neostigmine, a medication used to reverse neuromuscular blocking agents, used since 1939, UK HealthCare has seen the price increase 519 percent in 3 years. This was started in December 2013 when éclat-funded studies and gained market approval from FDA. The FDA allowed other agents to enter the market, and in November 2015, the price increased further to 127 percent. In January, Fresenius Kabi also funded studies, receiving market approval. The price increased further in February 2015 to 519 percent, and it stayed there despite a third manufacturer, West-Ward, in December 2015 gaining FDA approval.

With vasopressin, a medication used since the 1950s in the treatment of vasodilatory shock, a single manufacturer gained FDA approval in 2014. Since then, the other generic manufacturers have dropped out, leaving only one manufacturer of a critical medication, which puts patients at risk in case of a national shortage. The price increased 3,362 percent in 2 years, and in the same time period, UK HealthCare has spent approximately $650,000 more on this medication.

As a result of this initiative, medication spend has increased. However, these are the same medications that we have been using in the hospitals for decades.

The change in ownership effect that has been seen with acquisitions of drugs like EpiPen is also impacting medications used specifically in the hospital setting. Nitroprusside saw price increases of 1,745 percent following Valeant's acquisition of this medication. Calcitonin injection saw a price increase of 1,258 percent and then again 3,259 percent in a period of 2 years following Mylan's acquisition of this medication. Unlike the FDA initiative, these manufacturers have not invested any dollars in R&D.

A phenomenon that has been reported in the retail environment over the last 2 years is a sole source effect seen with many generics. These are typically older generic medications that have fallen out of favor due to other novel therapies. As manufacturers leave this market and only one or two remain, we are seeing skyrocketing price increases. This is impacting many patients who use older generic medications based on their affordability.

Potential solutions to these issues include introduced legislation such as Senate Bill S. 3335, the Fair Drug Price Act of 2016, as well as asking FDA to consider performing an analysis on the market impact of the Unapproved Marketed Drugs Initiative thus far.

Regarding the PBM 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 two-pen EpiPen is $608, Mylan only receives $274 net revenue on the transaction. Questions should be asked as to where the remaining $334 go. Lack of transparency will obscure where every dollar goes. However, given the rapidly increasing profits of the larger PBMs, questions should be directed in this direction.

PBMs have evolved since the 1970s such that we have seen unprecedented growth in consolidation, decreasing transparency, and conflicts of interest develop with PBM-owned mail order and specialty pharmacies. Introduced legislation that could improve transparency in this sector of healthcare are House Bill H.R. 244, the MAC Transparency Act, and Senate Bill S. 3308, Improving Transparency and Accuracy in Medicare Part D Spending Act.

Thank you for the opportunity to provide testimony today.

[The prepared statement of Mr. Almeter follows:]

PREPARED STATEMENT OF PHILIP J. ALMETER, PHARMD

Thank you, Senator Paul, and members of the Committee for the opportunity to provide testimony today regarding the rising medication prices in the United States. 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 fiscal year 2016 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 5 years spend with specialty medications has doubled contributing to 70 percent 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 percent 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 grand fathered 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 percent in 3 years.

- Originally patented in 1933 and approved in the United States 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 nondepolarizing neuromuscular blocking agents after surgery.
    - FDA allowed time for other agents to enter the market.
- November 2015—Price increased 127 percent.
- January 2015—Fresenius Kabi, following funded studies, received FDA approval to enter the market.
- February 2015—Price increased further to 519 percent.
- 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 percent higher.
- **Impact:**
    - Compared to fiscal year 2014, UK spent $243K more in fiscal year 2015 and $259K more in fiscal year 2016.
    - 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 fiscal year 2015 and fiscal year 2016.

- **Vasopressin:** Observed price increase of 3,362 percent in 2 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 percent.
    - April 2015—As other generics begin to drop out of the market price increases 2,321 percent.
    - January 2016—Price increases 2,787 percent.
    - July 2016—Price increases 3,362 percent.
    - **Impact:**
        - Compared to fiscal year 2014, UK spent $194K more in fiscal year 2015 and $452K more in fiscal year 2016.
        - 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 fiscal year 2015 and fiscal year 2016.

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 percent in less than 2 years.
  - Since 1988 Hospira has owned and produced.
  - December 2013—Marathon acquired and the price increased 350 percent.
  - February 2015—Valeant acquired and price increased 1,250 percent.
  - July 2015—Valeant increase price 1,438 percent.
  - August 2015—Valeant increased price 1,745 percent.
  - **Impact:**
    - Compared to fiscal year 2014, UK spent $194K more in fiscal year 2015 and $104K more in fiscal year 2016.
    - 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 fiscal year 2015 and fiscal year 2016.
- **Calcitonin Injection:** Observed price increase of 3,259 percent in a little over 3 years.
  - Since 1986 Sebela has produced this product.
  - August 2014—Increased price 1,258 percent (from the price in January 2013).
  - September 2015—Mylan acquired the product.
  - March 2015—Increased price 2,823 percent.
  - May 2016—Increased price 3,259 percent.
  - **Impact:**
    - Compared to fiscal year 2014, UK spent $451K more in fiscal year 2015 and $390K more in fiscal year 2016.
    - 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 fiscal year 2015 and fiscal year 2016.

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 2 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 2 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

Generic medication	Percent price increase 2014–2015
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 Senator 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 percent or more increase in price over a 12-month-period.

Additionally, consideration should be given by the FDA on analyzing the market impact of their Marketed Unapproved Drugs Initiative thus far. If the two medication examples listed above increased expenses in excess of $1M in a 2-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 United States 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 United States 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 percent 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 percent increase) in a span of 10 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 adjudica-

tion (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 Senator 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.

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Senator PAUL. Thank you.

Our final witness—and then we'll have some discussion—is Jim Waters, who is the President of the Bluegrass Institute for Public Policy Solutions.

STATEMENT OF JIM WATERS, PRESIDENT, BLUEGRASS INSTITUTE FOR PUBLIC POLICY SOLUTIONS, LEXINGTON, KY

Mr. WATERS. Thank you, Senator. Good afternoon.

As Senator Paul said, I'm with the Bluegrass Institute for Public Policy Solutions. We are now celebrating our 13th year. We were founded in 2003 as a State-based free market think tank.

Whether we're talking about manufacturing or education or healthcare or the development of new drugs, it's vital that we do understand that the free market does work when it's allowed to do so. Competition, as we've heard, drives innovation, and perhaps nowhere is that innovation more important than in the area of research and developing drugs that save lives.

I'd like to tell a short story that I shared with 1,500 freedom fighters at the State Policy Network to show that while there are risks and while regulators often claim that they're looking out for us and that they are being compassionate, the consequences of placing unmovable barriers to lifesaving drugs is the wrong approach, as it actually does end up costing rather than saving lives.

Once upon a time, an eagle's egg was knocked loose from its nest, and it rolled down the mountain into a barnyard full of chickens. Intending compassion, these chickens committed to protecting that egg until it hatched, after which they raised this creature, not as a beautiful eagle, but as just another chicken who scratched for grubs and worms and flittered around the barnyard.

One day, a neighbor convinced the farmer who owned these chickens to let him take that eagle up the mountain and see if he could fly. When that man released him, of course, that innate desire to live free and soar took over, and that majestic bird stretched his wings and flew into the sky.

What if he hadn't? What if he had fallen to the ground and died? Would anyone dare claim that that neighbor had done evil in giving that eagle the opportunity to fly? Should we really have kind of a rope-a-dope drug approval system that says no, even to seriously ill or terminally ill human beings' right to try every option to save their lives, even if in the end it doesn't always work?

What if medical missionary Dr. Kent Brantly had died of that humiliating wasting disease of Ebola, even after taking ZMapp while in Liberia, where he was 6,000 miles from family and utterly alone? Sure, he had a right to know that no human had ever been tested and that it hadn't fully passed all of the FDA safety protocols, which had been going on for years with that drug. Who should have told him that he had no such right to try it until some government agency finally got around to approving this drug, even as he stood close enough to death's door at age 33 to push it open?

Who had the right to deny Kalamazoo College sophomore Emily Stillman the opportunity to try a vaccine against meningitis that was available but not yet approved by the drug bureaucracy, even after years of testing and trials. Too often, bureaucracy has cried in Chicken Little fashion, "the sky might fall," while denying the Emily Stillmans of our world the right to try and save a life, her life, as if that life belonged to some government agency.

Yet no government agency blocked Dr. Brantly's access to the experimental ZMapp and the ensuing miracle which finds him today fully healed and still serving the world's poor and downtrodden. It's a moving story, don't misunderstand. I'm very happy about what happened to him and for his family. What about all the others that also had a right to at least try? Who also could have lived a miracle?

Twelve hundred people make it through the FDA's Compassionate Use Application each year. The process is so complicated. It's very time consuming and extremely expensive. Plus the FDA keeps no record of the many, many people who try but who are denied that application. The first step in that process alone is laborious. It requires a physician to complete an application to the FDA that takes around 100 hours just to fill out, after which the manufacturer also must submit lengthy documentation requirements.

The FDA then has a month to review the submission and either grant or deny the request, and if there are any questions at all, that 1-month clock starts completely over from the very beginning. After the FDA approves a request, a separate committee not affiliated with the FDA, called an Institutional Review Board, also must approve the patient's use of the drug, and this board can also take up to a month to reach a decision. What do you think happens a lot of times during that process? Sadly, there are many documented cases of patients dying while their application is being considered through this process.

While the FDA claims these regulations are needed to protect lives, in the end, they are too often costing lives. It seems like our government's experimental drug policy seems to have been more about control, about kind of picking and choosing, and EpiPen is a great example of this. Here we have a wonderful medical invention, and without the heavy-handed regulatory process currently enforced by the FDA, I'm convinced that other manufacturers would not only create a similar product, but an even better one.

Perhaps most disturbing about the EpiPen situation is that the FDA, at least at this point, as we've heard, has limited manufacturing of this lifesaving device to pretty much a single company, and the reason they do it is important to understand. They do it under the guise of ensuring safety. We want to make sure this is safe before we allow other manufacturing of these types of drugs. Yet this regulatory overreach has not only dramatically increased the price of the product because there's no competition, but it also discourages other manufacturers from developing better products.

This is cronyism at its worst, favoring a single company while shutting out other firms who would participate while also discouraging the research and development that would bring new, probably even better drugs to market. I would ask the question: Where is the compassion in forcing drug manufacturers through what

amounts to be a 7 to 10-year, up to a $2 billion process for some new drugs just to get them to the marketplace while people die who were willing to accept the risk of those drugs that may not have completely jumped through all the FDA hoops? It doesn't seem compassionate, and it certainly doesn't seem fair.

What if Dr. Brantly had taken ZMapp and then died anyhow? What if Emily Stillman had died even if she had taken the vaccine? Should that risk outweigh the potential of life restored? I have to ask: Should some government agency even be taking the temperature of such a risk with individuals willing to accept that?

An alternative ending to that parable that's often been used tells about how the eagle died in that chicken coop, having never been given the opportunity to try, never knowing that he could fly. Who knows the miracles that await by giving those even at death's crossing the right to know, the right to try, the right to see if they just might soar once again as well. It has happened, you know.

Thank you.

[The prepared statement of Mr. Waters follows:]

PREPARED STATEMENT OF JIM WATERS

Good afternoon. My name is Jim Waters, and I'm privileged to serve as president of the Bluegrass Institute for Public Policy Solutions, Kentucky's first and only free-market think tank, which was founded in 2003.

Whether we're talking about manufacturing, education or health care, it's vital that we understand that the free market works—when allowed to do so. Competition drives innovation. Perhaps nowhere is innovation more important than in the area of researching and developing medicines that save lives.

I'd like to tell a short story to illustrate:

Once upon a time, an eagle's egg was knocked loose from its nest and rolled down the mountain into a barnyard full of chickens. Intending compassion, these chickens committed to protecting this egg until it hatched, after which they raised this creature—not as a beautiful eagle—but as just another chicken who scratched for grub and worms and flittered around the barnyard.

One day, a neighbor convinced the farmer who owned these chickens to let him take that eagle up the mountain to see if he could fly. When that man released him, that innate desire to live free and soar took over. That majestic bird stretched his wings and flew into the sky.

But what if he hadn't? What if he'd fallen to the ground and died? Would anyone dare claim the neighbor had done evil in giving that eagle the opportunity to try?

Should we really have a rope-a-dope drug-approval system that says "no" even to terminally ill human beings' right to try every option to save their lives—even if—in the end—some of those lives do cease?

What if medical missionary Dr. Kent Brantly had died of the humiliating, wasting disease of Ebola even after taking Zmapp while in Liberia—6,000 miles away from family and utterly alone? Sure, he had a right to know that no human had ever been tested and that it hadn't fully passed FDA safety review, which have been going on for years. But who should have told him that he had no such right to try it until some government agency finally got around to approving it, even as he stood close enough to death's door at age 33 to push it open?

Who had the right to deny Kalamazoo College sophomore Emily Stillman the opportunity to try a vaccine against meningitis that was available but not yet approved by America's drug bureaucracy—even after years of testing and trial?

Too often that bureaucracy has cried in chicken-little fashion: "the sky might fall" while denying the Emily Stillmans of our world the right to try and save a life—her life . . . as if that life belonged to a government agency.

Yet no government agency blocked Dr. Brantly's access to the experimental Zmapp and the ensuing miracle, which finds him today fully healed and still serving the world's poor and downtrodden.

It's a moving story. Don't misunderstand. I'm very happy for him and his family. But what about all the others that also had a right to at least try? Who also could have lived a miracle?

Twelve-hundred people make it through the FDA's "compassionate use" application each year. But the process is complicated, time-consuming and expensive. The FDA keeps no record of the many, many people who try but are denied such application.

The process is complicated, time-consuming and expensive. The first step in the process requires a doctor to complete an application to the FDA that takes around 100 hours to complete, after which the manufacturer must also submit lengthy documentation requirements. The FDA then has a month to review the submission and either grant or deny the request. If there are any questions, that 1-month clock starts over.

After the FDA approves a request, a separate committee not affiliated with the FDA—called an Institutional Review Board—also must approve the patient's use of the drug. This board can also take up to a month to reach a decision.

Sadly, there are many documented cases of patients dying while their application is being considered.

It seems like our government's experimental drug policy has been more about control . . . about picking and choosing. EpiPen, for instance, is a wonderful drug. But without the heavy-handed regulatory process currently enforced by the FDA, I'm convinced other manufacturers could not only create similar—but better—products.

Perhaps most disturbing about the EpiPen situation is that the FDA has limited the manufacturing of the lifesaving anti-allergic reaction device to a single company under the guise of ensuring safety. Yet this regulatory overreach has not only dramatically increased the price of the product, it has discouraged other manufacturers from developing even better products.

This is cronyism at its worst—favoring a single company while shutting out other firms who want to participate and discouraging the research and development that would bring new and better drugs to market.

Where's the compassion in forcing drug manufacturers through what amounts to be a 7-to-10-year, $2 billion process while people die who were willing to accept the risk of drugs that may not have completely jumped through all FDA hoops? It's not compassionate, and it certainly doesn't seem fair.

What if Dr. Brantley had taken Zmapp and then died anyhow? What if Emily Stillman had died even if she had taken the vaccine? Should that risk outweigh the potential of life restored? Should some government agency even be taking the temperature of such a risk?

An alternative ending to that parable that's often been used tells about how the eagle died in that chicken coop, having never been given the opportunity to try . . . never knowing he could fly. Who knows the miracles that await by giving those even at death's crossing the right to know, the right to try, the right to see if they just might soar once again?

Senator PAUL. Thank you, Jim. I may have to steal that eagle story sometime. It's pretty good.

[Laughter.]

Jim mentions an ancillary issue, which is the right to try for people who are terminally ill, and there is a bill percolating through—I think 30-some-odd State legislatures now passed it—and I'm a cosponsor of it in the Congress, and we are trying to get that through as well.

We had some moving testimony from some patients with ALS, and one of the points that they made was that a lot of treatment for a new disease may well be specifically targeted to you and to the genetic mutation you have. There's said to be over 20 different mutations for ALS. It's not all the same disease, and perhaps maybe you're going to go to a lab, and some day, they're going to draw your blood, look at your chromosomes, look at your genetic defect, and they can't do a 1,000-person clinical trial on it because the treatment is going to be for you.

It kind of goes to Dr. Gottlieb's point that maybe we have to look at our criteria. Maybe what we used to do 20 years ago shouldn't be the same.

One of the most important things is when we're unhappy about something, that we look for the root cause and we don't blame the

wrong person. We're all unhappy, uniformly unhappy, at how the price went up by 500 percent, but there's a couple of different reactions. We could say, "Well, we need price controls. We just need to tell the companies they can only charge $100." Price controls were the disaster that brought down the Soviet Union and are the disaster that leads to poverty under socialism.

What we have to say—well, was this a free market? Was this really capitalism, as Dr. Strow was saying? Are there barriers to entry that are government? Are some barriers acceptable? Are we going to let the government be involved in some safety and efficacy? Probably, yes, but can they go too far?

The FDA, when we brought them in, they said to us, "Oh, you fixed this a year ago"—we passed some reforms about a year ago—and they said, "We're doing a lot better now," and I said, "Well, it's been 7 years. How about the EpiPen alternative?"

There are a lot of technical questions, and when you try to dig into this, if you bring the generic manufacturers in about these things, they're afraid to talk to us, because if I publicly state what any of the generic people are talking about—which they're allowed to tell me—they're afraid the FDA will punish them and will never approve their process. We ask the FDA, and they say it's proprietary—"We can't tell you any information about the applications."

It takes about four—3.7 times for the application to go to the FDA, come back, go to the FDA, come back, and 7 years is just, frankly, unacceptable. We do need to fix the system. With regard to EpiPen, it's both looking at people finagling or manipulating the patent system, and then it's also looking at speeding up the entry of new drugs into the marketplace, not only new drugs, but generic drugs.

One of the things that I'd like to ask Dr. Gottlieb would be with regard to—we had these reforms, and I know you understand the reforms. Do you think the reforms were enough? Do you think the FDA is doing a better job? There's some indication that the application time may not have gotten shorter since the reforms. They tell us one thing, and then we look at the statistics and it doesn't necessarily seem to be better.

Dr. GOTTLIEB. The statistics are getting better, because the cycling—they're trying to address the cycling. The overall length of time that it takes to review an application hasn't really gone down. They're reviewing more applications—they're getting more applications done within a certain timeframe, but they're still having these multiple cycles, and it's still taking a lot of years to get an application through. It's also too early to tell what impact the generic drug user fee law had on the process. It certainly gave them more resources.

With respect to this particular issue, though, there hasn't been anything that's resolved this issue of these complex formulations, and these, frankly, end up being a lot of the new and more innovative drugs and a lot of very important drugs. There have been other cases where there have been drugs where patents have long since lapsed, and FDA has struggled to approve generic versions to those drugs.

A classic example recently was lovenox. The lovenox patents were up for two or 3 years, and FDA was fumbling trying to get

the generic entrants through the generic drug approval process. It relates back to, again, trying to fit these complex drugs through that old generic drug application, that old generic drug process.

When I was at FDA, we were just starting to think about how we were going to approve generic copies of biosimilar drugs, and the FDA staff were arguing that they didn't need Congress to do anything. They didn't need new legislation. They could approve generic copies of biological drugs through a pathway called 505(b)(2) that existed. It turns out Congress did legislate, and thankfully, because if the FDA was struggling to try to approve these biologics through their traditional pathway or some nuance in the authorities that they thought they had, it wouldn't have gone as smoothly.

The same thing is operative here. The FDA will argue that they don't need new authority to deal with these complex drugs, yet they keep making mistakes when it comes to trying to introduce competition. They argue that they can put it through their traditional process, but, in fact, they haven't been successful at doing that.

This is a ripe opportunity for Congress to look at this whole category—to the extent that the category itself can be defined, and I think it can—and think of a sort of generic-plus type of approval process that's a little different than the traditional process but allows these drugs to enter the market more quickly.

Senator PAUL. Going back to whether or not this is broken capitalism or whether this is cronyism or what we should do, some will propose that we just need to cap the price and have price controls on drugs and that, somehow, that's the answer.

Dr. Strow, do you think this is a breakdown of capitalism, or do you think this is artificial barriers to entry from the government? What do you think of price controls?

Mr. STROW. Price controls generally make me squeamish, but I'm going to come back to that. I'm just going to start with the simple answer of, yes, it's largely due to barriers to entry.

Senator PAUL. Governmental barriers.

Mr. STROW. Government barriers to entry. Specifically, let's imagine a race. The gun is about to go off. We've got epinephrine or the EpiPen in one lane and a potential competitor in the next. The gun goes off. EpiPen takes off down the track, and you physically restrain the competitor and say, "You can't go yet. You have to start an FDA approval process, and 4 to 7 years down the line, we'll let you start running the race." You might imagine who's going to win that race, at a minimum, not just 4 to 7 years, but for some time after that.

The thing is with the patent system, we know when that gun is supposed to go off. We know when the patent expires—and we can go back and argue about whether or not we should extend patents—but we do know when the patent expires. If we know that's when the race can start between the brand name and the generic guys, why don't we let the generic guys go through all the product testing before the gun goes off? Why don't we hit it so that when the gun goes off, everyone gets to run? That would dramatically increase the role of generics in the market and bring them to market more quickly.

The overarching question we have to ask is: Does the FDA care about drug prices? We can argue that the reason they're set up is solely for drug safety, and if you're only looking at one end of the spectrum, then it's always going to be their incentive to have the safest possible thing, which is—safety is good, but they're not taking account of the tradeoffs.

The question is: In their charter itself, should they be forced to consider safety at what cost? All kinds of levels of government have to do cost-benefit analysis, and FDA, I don't think, should be immune from that.

I was going to hit on price controls. Let's take two scenarios. In one scenario, you're going to put price controls on for something that's patented. You just undid the patent protection. In another form, you either have a monopoly right to sell a product or you don't. If you come in on the back side and say, "Yes, we'll give you a patent, but"—wink, wink, nod, nod—"we're going to tell you what to charge," there no longer is that incentive to innovate in existence in the first place. You'd be effectively getting rid of the patent system.

The second question is: Do you want price controls for things that aren't subject to patents? Then the question becomes: Where is, again, the role of competition? Why would you need a price ceiling if new entrants could come in? We see from evidence in the drug industry itself and from the FDA, the evidence that they have collected, that when you allow the competition to happen, the competition does materialize and drug prices do fall. It would be a solution in search of a problem.

Senator PAUL. I like the idea of maybe starting a generic application process before it expires. If it's going to take you 4 years, if you took your 4 years before it expires, it wouldn't be as much of a complaint. All of us essentially acknowledge that we are not against patents and that we like the innovation that patents allow.

Particularly if we're going to reform this in ways drug companies may not like—but if you reform it such that you speed up the process of getting the patent and getting the approval, then they have a longer period of time to enjoy their patent protection. You could speed it up on the tail end, the transition to generics, but you could also speed it up on the front end so they can make more money on the front end if they can get their FDA approval sooner, which sooner FDA approval, if done properly, is what we want—lifesaving drugs more quickly on the market.

Does anybody else have a comment on Dr. Strow's comment on letting the generic application process start earlier? It doesn't start now, right? You have to wait until the end to file any paperwork?

Mr. WATERS. That would have a huge impact since 90 percent of all medicines filled in the United States are generic. Beginning that process earlier would certainly affect in a positive way—a lot of people.

Senator PAUL. I kind of wanted to broaden the debate beyond EpiPen, because Philip Almeter mentioned several of the drugs—so did Dr. Gottlieb—of all the different drugs. This isn't a one drug thing. There's a host of these and many of them in the generic sphere.

Sometimes we will ask: Why did everybody go out of business? We get these vague things, like voluntary recall or a manufacturing problem, and what I'm wondering is—and Scott may know this more than anybody else—is are they sometimes being told quietly by the FDA "You're going to get a public punishment. You can voluntarily do this, or you can say manufacturing problem." In reality, it's the FDA that is shutting them down by saying "You didn't pass a certain inspection."

Our understanding is that in the last couple of years—did something change to make it worse? Are there stepped-up investigations that are maybe knit-picking that really aren't going to the safety issue but are overwhelming some of the drug production, and then all of a sudden, we have no competitor because of an inspection process?

Dr. GOTTLIEB. Right. It is the case that FDA dramatically changed its enforcement standard with respect to what we call good manufacturing practices or GMPs as they apply to the generic drug industry, out of a perception not entirely untrue that the generic industry was operating at a different standard, in some cases a lower standard, than the branded industry, and they wanted to bring everyone up to the same standard.

They did that in a fashion where they went into these generic manufacturing plants and issued what we call 483s, which are findings of deficiencies, and the 483s become public and they create liability for the companies. If a company continues to operate a plant after it has received a sanction from the FDA saying that the plant is deficient in some significant way, that's a hard position to put a company in and for the company to continue operating.

What happened was they did this, and they knocked off the market 25 percent of the parenteral drug manufacturing in the United States. By parenteral drug—injected drugs, and these are a lot of the drugs that have been in shortage and where the prices have gone up. Last year, we almost had a shortage of normal saline in this country because they knocked the plants——

Senator PAUL. That was a reaction to the contaminated steroid injections that happened at the company—what, up in Massachusetts or something?

Dr. GOTTLIEB. I think it's actually the opposite. They did this prior to what happened in Massachusetts, and once these shortages were created by FDA for the branded drugs, more of the market shifted toward the compounded drugs, and that's why the utilization of the compounded drugs spiked. The FDA, by trying to address a risk in one context, actually increased the overall public health risk because more of the market shifted to less regulated products, the compounded products in the case that you referenced.

A lot of that manufacturing is not coming back online. The FDA has still imposed requirements on the generic manufacturers that are much costlier than what they used to be. For example, a generic manufacturing plant might produce hundreds of drugs in a plant and literally dozens on a single manufacturing line. The branded industry might produce a single drug or two on a manufacturing line. FDA is increasingly saying, "We want only a few drugs produced on a manufacturing line," because it makes it easier for them to oversee that manufacturing line. That's also very ex-

pensive, and it's not the expense at which the generic drug industry has traditionally operated. It's increasing the cost of the manufacturing.

When you increase the cost of manufacturing a pill that used to cost 2 cents and now it costs 3 cents or 4 cents to manufacture, that's a 100 percent or 200 percent price increase. There's a cost of goods component here as a result of the regulatory increase that's contributing to the price increases that we're seeing in the market.

Senator PAUL. I guess what we have to look at is in the mission that the FDA is given—are they going in and—have we increased inspections that are shutting down plants because of a problem, or are we doing it just because of an increased zealousness, that we have decided that we want to inspect these, and that perhaps it isn't improving safety? They've made a unilateral decision without a real problem.

Dr. GOTTLIEB. Right. My view has been it's a little bit of both, obviously, and there are situations where the FDA is on very firm ground in terms of shutting down a manufacturing facility. The larger problem is that there's a disconnect between the FDA field force that goes in and inspects these plants and issues these public findings and the policymakers back at FDA, the career staff who are more sensitive to considerations of what the real public health risk would be in allowing a plant to manufacture in some subpar State versus taking the manufacturing offline and creating unintended consequences.

The policymakers in FDA have a very hard time getting control over the field force. The field force operates as sort of an independent law enforcement unit and doesn't really respond to those policy prerogatives. They'll go in and shut a plant down, even if the policymakers might say, "Look, we would rather that plant continue to operate under close supervision while they remediate themselves because we don't want to precipitate a shortage that might force doctors and patients to have to use a compounded alternative that we know is a lot less safe."

That kind of teaming of those two regulatory pieces of FDA isn't happening. The only place it is happening is on the biologic side, and that's in large measure because after we had those shortages of the flu vaccine that you'll remember, you saw long lines in Florida because the FDA shut down some flu vaccine manufacturers right before flu season. CBER, the Center for Biologics, adopted what they call team biologics, where they basically forced the field force and the review staff to work together on these inspections, and so you had inspections happen that were much more sensitive to what some of the potential consequences would be of shutting down a facility.

That's not happening as much on the drug side. You're seeing unilateral decisions taken by the field force to shut certain facilities or force their shuttering, and then the consequences are felt by the career staff at FDA who worry about the unintended consequences.

Senator PAUL. I want to go back briefly to what Dr. Gottlieb said earlier. Neither side will tell us—the FDA or the people making the generics—exactly why it hasn't been approved. There are articles out there saying that it's not enough the same.

The question I asked to the FDA was, "What does that mean? Have you defined a sameness standard?" They said, "We're working on it." Companies have gone through 7 years of being denied, and there's no written standard of what the same means. I say, "Does it inject .3 milligrams, the same as the EpiPen?" They won't tell you that, either, but I think the answer is yes.

I think it works. It injects the proper dose. It's not harming anybody. It may be that the instructions aren't exactly the same, and I was like, "Are you telling me that if the spring that launches the needle is a right-handed spring versus a left-handed spring, it wouldn't be the same?" They were like—essentially, yes.

It's a distinction without a difference that's stopping things, so they're screwing up a whole marketplace, making us wait 7 years for competition based on something that actually works. The catch–22 is they're saying it's not enough the same, but if it's different, then give them a patent. Give them a patent for a brand new device. Then they'll be sued also.

What happens is every time a generic wants to come on the market, they immediately get sued by the patented every time, and then there's a 30-month waiting period. We're looking at maybe shortening the 30-month waiting period. They're going to sue them every time. Why don't we shorten it and make it 12 months or 15 months?

I'm of the belief that we need more oversight of the FDA, and the last time around—they want to put soft words in for the FDA, like they may do something. I want to say that they shall do something. They need more oversight from us, because left to their own devices, they don't have a good track record. I guess you could argue that for safety, we have done a pretty good job in our country.

I wanted to see if anybody else knew anything about the tetracycline problem or some of these other drugs. Maybe, Philip, you can comment on this. They say there's a shortage of the base ingredients going into tetracycline, and I don't see a shortage in any other marketplace. I don't understand how when you order it—if you go to Walmart and you take a water off there and you scan it, they know it's gone and they order more water. Unless it's a diamond or something, and there's a shortage of—tetracycline used to be for pennies.

A mother told me the other day it cost her $1,200 for a 1-month supply for her kid's—I think it's doxycycline or minocycline—but a tetracycline—it's been generic for 50 years probably. Even the derivatives are generic. Do you have any comment on the tetracycline?

Mr. ALMETER. No, the tetracycline shortages really occurred in 2011, and that's when we saw the real—the shortages spike across—hospitals were opening their totes in the morning and not seeing drugs in their totes.

Senator PAUL. Has the price come back down or not?

Mr. ALMETER. It hasn't. In January 2011, it was $6.76 a bottle for the 500 milligram capsules. Then in January 2013, it was $900, and then in May or June 2015, it's now $1,260 a bottle. There's only two manufacturers, Watson and Teva. Nothing else has

changed. It was short due to raw ingredients at the time, but nothing else has really changed.

Senator PAUL. I hear that, and I'm not sure—my warning signals of being suspicious about what I am being told. Shortage of supply. Why? Does anybody know?

Mr. ALMETER. I was going to say your question earlier to Scott regarding what's the message that pharmacies hear when all of a sudden something is unavailable—the example I gave earlier with the FDA Unapproved—with vasopressin and neostigmine, all we saw was messages from our wholesalers saying shortage issue, manufacturer's product issue. There were none of the details behind the scenes of "X manufacturer got approval, and we're getting pressure to get out of here or we're going to have fines put on us." You have to do a lot of digging. You have to ask representatives. They don't want to talk. A lot of it—you have to wait until it comes out in the news.

Senator PAUL. It's opaque. There isn't a transparency, and some it is this idea of proprietary knowledge. We're not hearing it from either side. One side is afraid of the FDA. The FDA says—and I understand the proprietary rules—"we can't tell you anything about it."

Like on the sameness thing, how do we fix that? The FDA is feeling some pressure now. They're going to actually define sameness. I asked them the same—some of these EpiPens have said it was a dosage problem. I want to know how far off it was. I want to know what a standard of error is. I want to know—was it doing .31? Was it harming anybody? What's the range? Can it go from .295 to .305? What is the range? They said they kind of have that, but they didn't seem to be very easy and forthcoming with it.

Then I asked them the question, "Well, did the EpiPen—what was its standard of error?" That's not really what you're comparing to. You're having to do new studies where you compare something to EpiPen, but the EpiPen may not have had—why wouldn't you compare it to an original study, that if EpiPen does .3, and it has a range of error on its injection, that would be the standard you would go by. But that, apparently, is not true. You have to go by new studies where you compare yourself to EpiPen. Right?

Dr. GOTTLIEB. To your point, initially, about the patent issue, Mylan was clever in this circumstance. They patented aspects of the auto injector that deal with how the auto injector itself is used. They created unique instructions for use for their auto injector and then patented the aspects of their product that deal with those instructions for use.

Senator PAUL. Maybe we should stop that—stop allowing a patent for that, because there is some discussion—like I remember in ophthalmology, some guy patented the frown incision. We used to do the smile, and he turned it upside down and it was a frown. Everybody made fun of it somewhat, but I think he actually got a patent. Maybe you shouldn't be able to get a patent for——

Dr. GOTTLIEB. Just change the regulatory standard, because the regulatory standard right now is if it requires any retraining by the patient, then it can't be a generic alternative. I would argue as a clinician, a little bit of retraining, if it's self-explanatory to the patient, might be permissible and might be perfectly fine and isn't

going to confuse the end user. Maybe we could provide a little more flexibility there.

Senator PAUL. One other thing I'd like to say—and then we're also open for a couple more questions and responses here—is that I'm a big believer in trying to figure out the problem. You don't just get angry and put price controls on. You figure out the problem—and this is a complicated issue—and then we figure out how to fix it.

All of you have taken the time to come and testify. I know many of you had to drive hours or come from other States, and I appreciate that. We want to find the solution. If any of you are willing to continue to work with our office—several bills were mentioned, and we know about some of those, and we will continue to look at those.

Also, we'll be looking at a solution. I'm going to work with Chairman Alexander to try to find a solution to this. As this comes forward, it may take 6 months, it may take a year, but we want to actually try to fix some of this stuff. Maybe we don't patent labeling, maybe we define—if they tell us what they think sameness is, maybe we tell them, "No, this is what it should be," and when they say there are manufacturing issues, we would say, "Have you pushed them out of the market?" Do we make it easier when there's one supplier? If someone gobbles up all the suppliers, should we make it easier?

Apparently, they do have a special route for drugs to come in, to be imported, if there is said to be a shortage, but they don't have it for single supplier. Maybe we should do it for single supplier. Some of this has to do with drugs coming across foreign boundaries, which maybe we should enhance. We're not the only civilized country in the world. Europe, Asia—there's a lot of places that do testing. Should we not have a more international system of trying to approve drugs?

Does anybody have another comment on any of the issues or want to make any other statement?

Mr. WATERS. I'm concerned that we discourage the continuation of research and development with barriers. Part of our system is trial and error a lot of times. In the development of these drugs, sometimes you don't always get it on the first swing. You don't always hit it. The companies have to be encouraged to continue to research that, and maybe a lot of these regulatory barriers have been detriments to that part of the process that we don't see.

Senator PAUL. We're going to conclude, but I talked to Courtney earlier.

Would you mind just standing up and tell us who you are and a little bit about your kids and their problems?

AUDIENCE MEMBER. My name is Courtney, and I have two children that have food allergies and require an EpiPen. I've been with—Laura Jackson's e-mails. There have been many meetings, I follow this closely. The main concern is the unexplained price increase. We switched over to the Auvi–Q and it was great, because I have a teenager and he liked being able to carry it. It was perfect for him.

Then right after the Auvi–Q was inexplicably recalled, the prices jumped. Before, it was costing us, with a co-pay, around $50. Then

we were without insurance, and we were on a bridge insurance for the summer, the Kentucky Connect health insurance policy, so we started paying about $250 for a set of EpiPens. I have two children and that was a cost of $500 that I couldn't afford, and my parents, luckily, stepped in and helped me pay for that. Then my job started and I got insurance, and my co-pay was reasonable.

Without insurance, right now, my EpiPens for one child would cost $802, and—as you said, it was lower. I've tried to find out why the Auvi–Q has been recalled, and there isn't a lot of information about that. I understand what you're saying about how the pharmacist is not given any information, because when I asked him, he said, "Well, it just says it was an insufficient supply or delivery method." I don't think there's been any record of anybody finding any injury, any adverse effects from using an Auvi–Q.

Competition is good, and if you could eliminate some of these barriers, maybe we would see that it's helping competition.

Senator PAUL. Thank you. That reminds me of one more question for Philip.

The one that's out there is Adrenaclick. Is Adrenaclick significantly cheaper for you at the hospital than EpiPen?

Mr. ALMETER. The one we use at the hospital costs a few dollars, because we use a vial and we're giving it in a code situation intravenously.

Senator PAUL. You're not using an auto injector?

Mr. ALMETER. In the retail environment, we are buying the generic, as well as the brand. I guess it depends on the plan, the payer and what the patient——

Senator PAUL. It's complicated to figure out whether the price——

Dr. GOTTLIEB. The list for Adrenaclick is $140, the list price.

Mr. ALMETER. It's about $400 for us to buy.

Dr. GOTTLIEB. The Adrenaclick is $400?

Mr. ALMETER. The Adrenaclick is about $400.

Senator PAUL. Which gets to the whole other question—there's 10 different prices, and it's so confusing, and then there's rebates for big purchasers, et cetera, et cetera. For you, you say the price is not that much different?

Mr. ALMETER. No, it's about 8 percent cheaper for the generic.

Senator PAUL. I think what's happening is he's a much bigger purchaser than you.

Mr. ALMETER. Sure.

Senator PAUL. EpiPen is probably offering a steeper discount to try to get you to use it. There's not enough differential for you to even—if you have a differential in the hospital, will you try to encourage your physicians to order cheaper varieties if you think they're equivalent?

Mr. ALMETER. It's really dictated by the plan. That's really where it's——

Senator PAUL. By the plan, more than the physician?

Mr. ALMETER. Yes, it really is, and it's a safety net provider when they can't afford it. I will say this, that UK HealthCare—we're a safety net provider. We have to get the drug to the patient, and if they can't afford it, we will use our dollars to give it away for free.

Senator PAUL. Right. Some of the published material also said that Adrenaclick was not therapeutically equivalent to EpiPen. Does anybody know what that means? I know what it means, but why are they saying that.

Mr. ALMETER. My understanding is it has to do with AB rating. If you look at the rating, it's a BX rating, and they won't say that they're perfectly bio-equivalent.

Dr. GOTTLIEB. It's not substitutable, but it would have to do with the device, not the drug inside the device.

Senator PAUL. Once again, sort of a distinction without a difference. It gives the same dose, and it probably works equally as well, and you could debate which one works easier or better. By saying that, what's happened on some insurance plans is some insurance plans have listed it as a second tier, where they would rather you get the other one because it's the gold standard and this is not therapeutically equivalent.

Mr. ALMETER. Or they get a bigger rebate with that one.

Senator PAUL. Exactly, and that's another problem we're going to look into as well. We've gotten a lot of answers today, and we're going to keep looking into it. We want to keep in contact with you, if you'll keep in contact with us, and we would appreciate any of your feedback.

Thanks, everybody. I'm supposed to adjourn us here.

I'm sorry. If you have any more comments, you can put them in writing, and we'll put them in the record. What you've given us as your testimony today will be in, and you have 10 days to submit anything else.

Thank you for being here today, and the committee will stand adjourned.

[Whereupon, at 4:10 p.m., the hearing was adjourned.]

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