Balancing the Promise and Cost of Biotechnology
The Alliance for Health Reform and Health Affairs
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ED HOWARD: Greetings. My name is Ed Howard. I'm with the Alliance for Health Reform. On behalf of our chairman, Jay Rockefeller, our vice chairman, Bill Frist, and the rest of the board, I want to welcome you to this program on the policy implications of biotechnology. Our partner in today's program is *Health Affairs*, the world's most respected health policy journal. We're very pleased to say that if you haven't gotten one, you should get one. The current issue of *Health Affairs* is available for you for taking the trouble to attend this briefing, and you should make sure that you have that because it has a collection of articles on today's topic, as well as a bunch of other things unrelated to that topic, which I know will be of use to you in your work. As a matter of fact, let me start by yielding the floor to the founding editor of *Health Affairs*, John Iglehart – John?

[Applause]

JOHN K. IGLEHART: Thank you, Ed. Welcome and thank you for coming. This biotechnology issue, which we published this week, was about a year-and-a-half in the making. It was a subject we hadn't really delved into in the past, but in the year-and-a-half we worked on it, we clearly had the sense that – as we've used in the title – biotechnology has come of age, not only as an industry, but as a set of medical

innovation companies that are making a difference, and a large difference, in the lives of many Americans that need the kind of products that they are producing.

I would like to introduce Lisa Payne-Simon, who is in charge of activities at the Blue Shield of California Foundation that relate to medical technology broadly. It was the Blue Shield of California Foundation that was the major supporter of this thematic issue. So I want to acknowledge their contribution to this event and give Lisa an opportunity to say a word or two about the kind of interest in the broad area of medical technology that this foundation is focusing its grant-making on. Lisa?

LISA PAYNE SIMON: Thank you and good afternoon everyone. The Blue Shield of California Foundation is an independent, nonprofit grant-making organization based in San Francisco. Through grant-making, we support innovation in health care policy and delivery system efforts to improve evidence-based coverage and decision-making, and also efforts to advance evidence development for new medical technologies. We also support technology assessment for new medical technologies through our operating program, the California Technology Assessment Forum.

This issue of *Health Affairs' Biotech Drug Comes of Age* is an exquisite example of the kind of innovative,

thoughtful guidance in the field that we aim to support through our grant-making, and we are very proud to be a part of this effort.

Biotech is particularly challenging because of the intense dynamics of patient demand for potentially life-saving drugs and procedures that are also, at the same time, extremely costly and for which evidence is not always available. So this creates an excruciating dilemma for policymakers and other health care decision-makers in terms of how best to proceed. The kinds of guidance and insight that this issue lends to this topic is of extreme value to the field and to all of us, so, again, I'm very proud and The Blue Shield of California is very proud to be a part of this initiative. Thank you.

ED HOWARD: Thank you very much, Lisa. Let me just handle a couple of logistics. Those of you who have been to Alliance briefings in the past know a lot of this, but we want to make sure that everybody does – that is, to say in your packets you have a bunch of background information, in addition to the *Health Affairs* article, and there are, among other things, in that packet more extensive biographical information that you're going to get from me about our speakers, closer to what they deserve. By tomorrow morning, you'll be able to watch a webcast of this session on

kaisernetwork.org. On both that Web site and ours, allhealth.org, you can find the materials from your packets in digital form that you can share with more people if you would like to. You will see a number of microphones scattered around the room. You'll be able to use those to ask questions at the conclusion of our formal presentations. There is, in your information packets, as usual, a blue Evaluation Form that we would very much like for you to fill out so that we can improve these programs for you in as efficacious of a way as we possibly can.

We have a really excellent line up of speakers, with both analytic and stakeholder views very well represented. Let's get to that before we lose the momentum that we've already generated.

We're going to start with James C. Robinson. He's the Kaiser Permanente distinguished professor of health economics and chair of the Division of Health Policy and Management at the University of California, Berkley, School of Public Health. Jamie chairs the Health and Policy Program at the Goldman School of Public Policy there and is a core faculty member of the Health Management Program at the Haas School of Business. He is a former panelist at Alliance briefings and he is back by popular demand. He is the author of the theme article in the *Health Affairs* issue that you

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have in front of you. We're very pleased to have you, Jamie, thanks for making the trip.

JAMES C. ROBINSON: Thank you, Ed. I'm certainly very pleased to be here. Biotechnology is a rapidly growing and central part of the health care system going forward. It's great for its patients, it's great for the larger economy as a science-based, capital-intensive source of high-wage jobs in the economy. The challenge it poses now – at its moment of success where it has a lot of products really coming onto the market for a lot of indications – is that the revenues from those products, which are financing further R&D and new products, is booked as cost for the insurers and, behind the insurers, the employers, governmental agencies and individual employees who are paying insurance premiums.

What I want to do is briefly talk about the current state of the strategies in the private insurance sector to evaluate and manage the use and costs of biotechnology products, biopharmaceuticals. Under the global framework – if you will – that a dynamic, innovative industry requires many things, but one of them is a sophisticated purchaser. Smart purchasing leads to continual pressure for better-quality, higher-value products and we're groping towards that balance between. We've got a sophisticated industry, and

we're groping towards a more sophisticated purchaser of those products.

ED HOWARD: I just wanted to tell folks that we don't have hard copies of Jamie's slides in your packets. We weren't able to get to them in time. We will have them posted on our Web site so that you can make copies at that time.

JAMES C. ROBINSON: I want to talk very briefly the challenges posed by biotechnology from the perspective of the payers and the strategies, in terms of choice of product, product pricing, site of care and future directions.

Obviously, the challenges are quite straightforward. Biotech products are still a small part of overall costs – about 1-percent – but they're rising very rapidly at about three times the rate of overall cost, and costs in general are rising much more rapidly than productivity and worker wages. This is the general thing – the rising costs are a challenge to the insurance system and, behind them, to the individual employees.

The employment-based insurance system is eroding due to the cost rise. Medicare and Medicaid are absorbing a lot of that enrollment, but from the provider perspective, there is a great fear of rounds of cutbacks in payment rates. So

the basic message to the insurance industry from their clients is to moderate the cost trajectory. That is the number one thing that is going on out there.

Most of cost growth in health care, as we know, is based on good stuff. It is new drugs, new devices and new procedures. Most of this stuff is good stuff, it works. If it weren't, we wouldn't have a problem. We would simply not pay for it and that would be the end of health care cost inflation. But, in fact, a lot of this stuff does work. We've seen dramatic improvements in the care in cardiac disease, with the beginning of transformation of oncology from a fatal, acute disease to a long-term, chronic disease like AIDS. There are a lot of victories, but this is the big challenge. From the point of view of the purchaser, you don't want to say no to this stuff. On the other hand, the insurers are concerned about patterns of inappropriate use, they're concerned about the prices of the products, and they're concerned about the misaligned incentives in the utilization of the products. I will be talking about each of those – choice of product, pricing and site of care. We'll just role right through this.

The first stage is always formulary management. Health insurers – the private plans and also Medicare – have a list of products that they will cover and those that they will not cover. For those that are covered, some are covered

unconditionally and some of covered with conditions. The evidence base underlying most biologics products is stronger than the evidence base under most of medical care. There is simply no question that these products have been subjected to a lot of the best-quality clinical review when you compare to a lot of things that Medicare pays for and that private insurers pay for. Having said that, there is inadequate information on comparative efficacy. When a new product comes down the line, how does it perform, not compared to placebo, which is the usual test, but compared to the standard therapies for comparative efficacy and side effects? For which indications should it be used? Usually things are approved by the FDA for a particular indication and then the physicians are, of course, allowed to prescribe any drug for any condition under the scope of their medical license.

There can be non-coverage but, essentially, as far as I can tell, there are no cases of non-coverage of biologics for FDA indications. There is simply no health plan that is going to do that. It would just be a public relations disaster, as well as a bad thing for their covered patients. They just don't do that. The issues are, though, for which patients? Prior authorization is a basic tool that says for services, including drugs or devices or procedures, for which there is evidence of inappropriate use, the provider that prescribes them needs to get prior authorization from the

health plan in order for there to be payment. Not prior authorization to do the treatment or prescribe the drug, but to get payment for the drug, which is very important. Basically, what they want to know in these prior authorizations is whether this thing is being prescribed for a patient that has a condition that this product treats. You would be amazed at how much stuff is being prescribed for conditions that there is no evidence that that product treats.

Step therapy is an approach that says the product can be used, but only after we've tried other strategies – typically cheaper therapies. For example, there's a very effective product, Xolair, which treats severe allergic asthma. It's a very good product, but a very expensive product, moving patients from a few hundred dollars a year to $40,000 in maintenance costs. We want to make sure that the cheaper stuff doesn't work. So for those patients where the cheaper stuff fails, fine, move them ahead. But for those people where the cheaper stuff does work, keep them on that. There is a big debate about limiting the off-label use, not in oncology where off-label use for cancer drugs is very widely accepted, but for other usages, particularly autoimmune.

The benefit design – as you all know, the general trend in benefit design in insurance today is towards more

consumer cost sharing – it goes under the name of consumerism – more deductibles, health savings accounts and, in the pharma sector, tied formularies. Typically a three-tier where it's the lowest price for generics, medium price for formulary branded drugs and the higher price for non-formulary branded drugs, biological are overwhelmingly tossed into a now fourth tier where instead of having a co-payment like $10, $25, $50, it goes into a co-insurance co-payment, typically 25-percent. So there is a 25-percent exposure to often very high prices. We'll talk about that. Often these drugs are in the range of several thousand dollars per month.

The big question out there is to what extent is the total out-of-pocket limited, the out-of-pocket maximum? Unfortunately, out-of-pocket maximums are eroding. More and more patients are having open-ended exposure because their employer is not willing to pay for that. They're not willing to pay for the higher premium to have a limit on their exposure.

The prices – there is no question that the biologics prices are an order of magnitude higher than we've seen in oral pharmaceuticals. They were originally priced that high because the first biologics were for very small, narrow indications with very few patients, so-called orphan drugs. The prices have not come down as the indications have spread and as the number of patients has growth. There is very

little price discounting going on out there. It is a very serious issue. There is more and more of a cost on the unit prices of these products.

The strategies — Right now insurers are, frankly, very limited because with very few therapeutic equivalents and no generic or biosimilar or follow-on biologics on the market for all practical purposes, there is not an effective way to use a formulary to get volume discounts. It's most done via the use of prior authorization and step therapy mechanism, which are klutzy and everybody hates, but they are the only thing out there in terms of a version of formulary management.

The other issue is an attempt to limit the profitability of prescribing biotech drugs to the doctors. It's very different from most drugs. With most drugs, the doctor writes the prescription, you go get the prescription at the pharmacy, you pay the pharmacist and the pharmacist pays the manufacturer. The doctor doesn't make any money off the deal. The doctor makes a fee for his evaluation and the prescription, but not a percentage of the price of the drug. But in biologics, in many practices, particularly oncology, but also rheumatoid arthritis and autoimmune, essentially the doctor's practice buys the drug, gives it to the patient, then bills the insurer for reimbursement for the drug at a very substantial markup. One survey indicated that 70-

percent of oncology revenues in private practice on oncology come from drug markups, as opposed to from anything that the doctors do in their practice. So, obviously, from the insurer's perspective, they do not want doctors to be drug distributors. That's what they're doing is becoming – or they have become – small drug distributors.

Site of care – the big issue is that biologics have proven extremely effective when used appropriately. When used appropriately is mainly in very controlled trials, often in academic medical centers, but once they diffuse out into the general community, the patterns of care are all over the place. The basic trade-off is that the price of administering care is cheaper in community practices and more expensive in hospitals. Hospital outpatient departments are simply the most expensive places to administer these drugs. These drugs that are used [inaudible] are not the kind of drugs you put in your mouth. Some of them are pills, but most of them are infused or they're injected directed into the body because they would be destroyed, their proteins would be destroyed by the gut. They wouldn't be able to get through the gut.

The insurers want to encourage the continued broad use of these products in the broad communities, not just centralized in hospitals. A lot of that, frankly, has to do with the fact that in many communities in the country,

hospitals are very consolidated, have a lot of bargaining power and they are marking these drugs up very substantially.

Future options – first of all, better data, better coding – these things are very poorly coded in insurance claims and it is very hard for the insurers to find out exactly which drug was administered, in exactly which quantity, for exactly which condition in their claims data because of the way they are administered in the office, rather than through the pharmacy. They are very interested in much more data on drug non-response, adverse effects, cost effectiveness, et cetera, in the broad community, not in the clinical trial setting – we know that – but in the broad community. The goal is to have better guidelines to use and to hold the doctors to compliance prescribing within the guideline. That is an area of cooperation between the manufacturers and the insurers, because the manufacturers also believe in appropriate use of their product and support guideline use in most cases.

I just want to wrap up here with financial incentives. The future of this, from the insurer's point of view, is competition not between generics and branded drugs, but between multiple branded drugs in the same therapeutic category. Now that the industry is maturing we have certain niches – particularly in rheumatoid arthritis, multiple sclerosis and hepatitis C – where there are multiple branded

biologic therapies produced by different companies, which evokes the potential for formularies and for price negotiations around that. This is generally anathema to the industry. It's a list-price industry, but from the insurer's perspective, they want to do price discounting. More and more patients are moving into private plans under Part D, more and more Medicare patients. Needless to say, these are the patients that are taking a lot of these drugs and that buying power will flow through the private insurers.

On that note, I want to wrap it up and I would just conclude by saying that the private insurers' strategies for managing biologics costs right now are basically very elementary and not overwhelmingly successful. They're just trying to drive care more towards appropriate use, get rid of the fringes of inappropriate use, get the doctors out of the drug distribution world and then wait and hope that there will be begin to have more therapeutics in each class. Thank you.

ED HOWARD: Great, thanks very much, Jamie. I think that was a very thoughtful and broad-gauged look at how private payers are coping with this situation generated by the progress that we're seeing in biotechnology.

Now we're going to hear a little bit about what happens in the public sector from Sean Tunis. Dr. Tunis is

the founder and director of the Center for Medical Technology Policy in San Francisco and a principal at Rubix Health. He was previously the director of the Office of Clinical Standards and Quality and the chief medical officer for CMS, in which role he had lead responsibility for clinical policy and quality for the Medicare and Medicaid programs. In his article in *Health Affairs*, he lays out some of the strategies that have been developed, largely under his leadership, for those programs to deal with the challenge of biotechnology. Sean, thank you so much for being with us today.

SEAN TUNIS, MD: Great, thanks. I was just thinking, as I was listening to Jamie talk, about one of the first times I heard him presenting at a meeting. I remember sitting in the audience and thinking, "Well, thank goodness I'm not the person speaking right after him." [Laughter] So not only do I have to speak right after Jamie, but I actually have paper that comes right after Jamie's in *Health Affairs*. It pales by comparison. In any case, what I wanted to talk about – and I think it picks up off a lot of what Jamie was talking about – that essentially many of the strategies that payers are adopting to deal with the high-cost biotechnology products really, ultimately, for their success, will depend on there being reliable evidence of the risks, benefits and

costs of these products, particularly in comparison to other products.

My sort of punch line to all of this is we actually don't yet have a very robust research infrastructure to make sure that that kind of evidence is available for payers and patients, as well as physicians, who will be increasingly financially incentivized to make cost-effective decisions about these products. In order to get to a point where we're going to be using these in a kind of value-oriented and efficient way, we're going to need to build and enhance the enterprise that is producing this kind of data. Coverage with evidence development, which is being pursued by the Medicare program, is one mechanism to try to do that.

Let me just walk quickly through some of these slides. A lot of these points I think Jamie has touched on. This one – you probably all get tired of looking at these charts – is the unsustainable trajectory of health care spending. Some key points on this chart are that the annual per-beneficiary Medicare spending in 2005 is $8,000. In 2015, the Medicare trustees predict that it will be $16,000 and there will be a lot more of them. The thing I like to point out about this figure is that the definition of unsustainable is "cannot be sustained," meaning that that is something that will happen and something that is happening. I think a lot of the initiatives of the payers that Jamie

described are in recognition that these trends are unsustainable.

As was already pointed out, in sort of looking at these unsustainable trends within that, most analysts that have looked at this issue of what's the contribution of technology to increases in spending have determined that it is a major contributing factor, both new technology and new uses of existing technology. The consensus seems to fall somewhere in the 20- to 25-percent of increased spending in health care is due to technology. Again, also, as Jamie pointed out, this turns out to be a good value for money. I've seen different estimates of this, but by some estimates, for every dollar of additional spending in health care, there is $2 to $3 of resulting health benefit that emerges from that. Many would argue that that is a good value. The difficulty is that, again, the overall aggregate trends and costs are putting pressure on the system.

Within that, the biotechnology products, which themselves are only about 1-percent of aggregate spending now, are rising at sort of double-digit rates. The unit costs of these things are rising fairly dramatically. The overall spending is increasing. Technology is a big contributing factor and the biotechnology products are a major focus within that.

It is interesting to look at this slide. I'm not exactly sure of the time sequence here, but the old, basic treatments for colorectal cancer, the drug costs for two months for 5-FU and leucovorin rescue were in the range of $60 to $500 per two months. Then we had irinotecan and oxaliplatin added to the regiments – this is Camptosar and Eloxatin – and you get into the region of about $10,000 for two months. Now with Erbitux and Avastin getting all the way up to $30,000 for two months of therapy – so $15,000 a month for this combined therapy is obviously a huge step up. With this comes significant increases in median longevity with an increasingly number of two-year survivor for two-year metastatic colorectal cancer, but obviously at a tremendous cost.

Given all of this, this is where the payers have come to try to focus on, "Well, what can we do about this?" And they have built in the strategies that Jamie talked about. One of the ones I particularly want to focus on is this cost-shifting onto patients, which is fairly mature. What is probably coming down the line in the very near future is the sort of pay-for-performance, pay-for-efficiency and gain-sharing programs where physicians will actually have strong economic incentives to try to use these products most efficiently. The problem that they are going to face is that there are many questions about the risks, benefits and costs

of these products that are not routinely available. This is just a list of some of the kinds of things that are generally not answered by ongoing research, not just around biotechnology products, but medical technologies in general. Patients that are excluded from trials – we very much don't have information on those kinds of patients. What are the adverse event rates in real-world populations? What are the risks and benefits for the off-label uses of approved products which, in some cases, become very prevalent? And then there are issues about the relative effectiveness of one product versus another, combinations of products and sequences of products. Now you have four products and more in the pipeline for colorectal cancer and really a very limited program, in terms of looking at which combination and which sequence gives you the best outcomes at the lowest cost? Then there is, obviously, comparative effectiveness within a category, which subgroups have the greatest benefit, and then there are often important clinical outcomes that are not measured in the regulatory FDA trials. So for every product, for every therapeutic area, there are lots of questions that are unanswered.

We can go into this more in the Q&A, but there are interesting reasons for why there are these gaps in knowledge about new and emerging technologies. Some of it is just, briefly, that NIH primary mission is on discovery and proof

of concept, not on comparative effectiveness, not on the so-called Coke versus Pepsi trials. Industry's focus is primarily on regulatory approval and market maximization. They don't tend to ask the question of "What's the optimal way to use my product given the armamentarium," because sometimes they don't want to answer to that question. ARC's role is to figure out what works, but they have a very modest budget and a very broad portfolio that not only includes these kinds of questions, but all of the quality measurement work, et cetera. Then there are lots of organizations that do systematic reviews of clinical research. For example, if you want to do a comparative effectiveness review of drug A versus drug B and no one has ever done a study of drug A versus drug B, the systematic review isn't going to really produce much useful information. I would assert that the reason for these systematic gaps in the evidence needed for decision makers is precisely because there is no part of the clinical research enterprise that is driven by the information needs of decision makers.

With that in mind, this is really the background and the inspiration for why Medicare tried to, as a major decision maker, become more active in deciding what kinds of clinical research studies would be done. The mechanism they used to do this was using their authority for deciding what is medically necessary to determine that in some cases a

medical technology would only be considered medically necessary in the context of prospective data collection. This was applied to implantable defibrillators, and it was applied to the off-label uses of all drugs approved for colorectal cancer. The idea is that perhaps we could use this coverage mechanism as a way to generate better prospective data about new technologies and answer some of these questions that patients and physicians need answered in order to make cost-effective decisions from amongst alternatives. Interestingly, I just learned earlier this week that UnitedHealthcare has actually adopted a CED approach to many of their anti-cancer biologics, as in now they will only pay for off-label use of these products if patients are enrolled in a data-gathering registry. So it's a kind of pay-for-data approach.

We've recently established, with support from Lisa Payne-Simon and the Blue Shield of California Foundation, as well as the California Healthcare Foundation, a nonprofit center that is located in San Francisco. Really what it is trying to do is create a private sector platform to pursue what Medicare was doing under CED, that is, to create a neutral, non-political platform for decision makers to come together and identify what the information needs are that would lead to efficient and effective use of new technologies. So what the center is doing is trying to

develop methodologies for determining what the priorities are from the perspective of health care decision-makers, develop inexpensive and rapid methods for doing better studies or the risks, costs and benefits of new technologies and then launching some pilot projects.

In addition to these things, there are lots of other activities going on to try to develop the evidence base for decision making around biotech and other new, expensive medical technologies. The Institute of Medicine has an evidence-based medicine roundtable looking at similar issues. There is a new organization that Steve Pearson is running called the Institute for Clinical and Economic Research that is trying to look at developing better cost effectiveness information. So I think there is a lot of growing activity in this area.

The bottom line of the story is that better evidence is key to preserving innovation in the face of spending trends. In other words, as payers and other policy makers try to do something about affecting these unsustainable trends in spending and focus on technology, I would argue that the only way that can be done in a sort of scalpel-like method, as opposed to a meat cutter, is having this kind of high-quality information for decision making. The current research enterprise is not providing all the evidence that is necessary to support decision making, so we need to expand

the capacity to do more decision-based evidence making in order to support evidence-based decision making. Thanks very much.

ED HOWARD: Nice turn of phrase, very good. Thank you so much, Sean. Well, the people who are creating what you might call the delicious dilemma of having wonderful tools that are a challenge to pay for are represented very well here today by James C. Greenwood. He is the president and CEO of the Biotechnology Industry Organization or BIO. I made the – I'm sure not original – observation that that is the absolute best acronym of any trade association I've every heard. BIO represents more than 1,100 biotechnology companies, academic institutions and other groups. Jim Greenwood has spent a dozen years as a US Representative from Pennsylvania's Eight District, including a stint as chairman of the powerful House Commerce Subcommittee on Oversight and Investigations. We're looking forward to hearing from the folks who are creating as many as – according to your web site – 200 new biotechnology products that can be used in a whole variety of disease situations. Jim, thanks for being with us.

JIM GREENWOOD: Thank you very much for inviting me. It's good to be here. Sean said that it was intimidating to

follow Jamie. I've been the CEO of this organization for a little over a year-and-a-half. I came from Congress, where you get by knowing a little about a whole lot of things. I suddenly find myself having to know a lot about a few things. I am happy to announce that I am the person with the least expertise on this panel, and Carolina will have a fairly easy task following me. [Laughter]

The title of this briefing is Balancing the Promise and the Cost of Biotechnology. I would submit, for starters, that we should be thinking about balancing the promise and the net cost of biotechnology, because, obviously, some of the drugs that we've been talking about so far this afternoon are saving us health care dollars by reducing the likelihood of long hospitalizations, expensive surgeries and so forth.

I spent 24 years – 12 years in the Congress and 12 years in the Pennsylvania Legislature – dealing with health care issues. The way policymakers usually think and payers and others about health care costs is they ask the question, "How much are we spending on hospitals, doctors, treatments and medicines?" In the year 2004, we spent $1.9 trillion on health care, $6,280 a person. Of that, we spent $571 billion of that was on hospital care, $400 billion on physicians and clinical services, $158 billion on nursing home and in-home care, and $188 billion on prescription drugs and, as we said, the biological are about 1-percent of the total cost. We

frequently find ourselves in what I call the iron rectangle of health care. There are four things that we fundamentally want for health care. We want quality, we want access, we want cost control, and we want innovation. If you look at the European and Canadian model, what they have accomplished there is they have absolutely knocked the access problem. It's universal and everyone in those countries has access to the health care system. They've done a pretty good job of knocking the cost issue because the government sets the prices for the products, so they can very readily control the costs. I would argue that the price they paid for solving the problems and demands of those two sides of the rectangles is that the quality is less than it is here in the United States and the innovation doesn't occur as robustly as it does in the United States. We, with our market-driven system, excel at quality and we excel at innovation, but we have 40 million plus people uncovered by health care. We have runaway health costs, as some of the slides have shown.

Policymakers can go about the process of saying, "What do we need to do to push down the costs of what we're spending on hospitals or doctors or medicines?" That is largely what they do. There is another way, though, to think about health care costs. That is to think about the cost of the disease. It is the disease that ought to be blamed for the cost of health care, not the products and services that

are used to produce health care. So you can look at it another way and that is to say that diabetes costs us $132 billion a year, cardiovascular disease costs us $300 billion a year, cancer costs us $210 billion a year, stroke is projected to cost $2.2 trillion over the next 50 years as the population ages. I think what is important to understand is that sometimes we look at controlling health care costs by lowering the price that we pay for health care services. Sometimes, but not nearly enough, we look at how we can reduce health care costs by taking a preventative approach. We do that in a relatively paltry way by periodically extending coverage in the public and private sector to screenings and preventative care, but not nearly enough. I would argue that the real promise of biotechnology is that it gives us the opportunity to ultimately escape that rectangle, that iron rectangle, in which it always seems that quality is the enemy of cost and price control is the enemy of innovation. We're clearly moving through the gains in biotechnology at a faster rate every day towards a predictive, a personalized, and a preventative system of health care. What biotechnology gives us increasingly is the ability to do more sophisticated screenings and diagnostics to identify the susceptibility or the predisposition to diseases to being prophylactic treatment long before the disease expresses itself. We're able to use personalized

medicine using genetics and biomarkers to select the right patients – not everyone gets the expensive products – and the right dose at the right time. We're literally fast approaching a time in our history where we are able to block disease at the cellular level, at the genetic level and at the molecular level. The danger, I think, is that we forgo this promise. By that, I mean literally the promise that when a child is born, the child's genome is sequenced, that the proclivities for various diseases are identified and that, by using the most advanced techniques in biotechnology, the genetic causes of causes that have plagued mankind forever can literally – the genes can be shut down from expressing those diseases so that the diseases never manifest themselves to begin with. If we are increasingly able to prevent diseases from expressing themselves to being with because we understand at a very precise level the biology and the causes of those diseases, if we understand at a very precise level how to make products that prevent those diseases from occurring, then, in fact, we go after the real villain in the story, and that is the price of disease itself. By doing that, we dramatically reduce health care costs, we expand access and we still continue to enjoy quality and innovation.

If, instead, we focus on price controls and thereby prevent the biotechnology sector from arriving at that day

that I've described, we will have truly lost one of the greatest opportunities that mankind has to improve our condition. I think it does make sense when we look at the cost of drugs to also look at not only the price of the drug, but the cost of producing that drug. Why is it so expensive? Why does it cost $800 million to $1 billion and growing to bring drugs to market? Are there different paradigms for doing clinical trials, using the knowledge we gained from biotechnology to, in fact, dramatically reduce the costs of development of the drugs?

The first transatlantic telephone call made from New York to London, I think cost about $100 a minute. If Congress had decided to step in and say, "That's an outrage. We cannot afford that. We're going to control the price," we'd probably still be making that call on one of those wind-up telephones. In fact, in a relatively short period of time, the price of that call went to $10 and I think it is now about $1 a minute. That was because the revenues that were generated by that technology were looped back into innovation, which produced more and more efficient, more and more precise technology, which is why we all carry Blackberries and telephones that take pictures and send video and so forth.

There's one other point that I will make and I can probably take it in questions. There is an argument that

follow-on biologics, biosimilars, generic biologics – choose your term – will, in fact, be able to dramatically bring down the costs of these products. That remains to be seen. In fact, there is a very good body of evidence that say, number one, because a biologic is not a chemical compound you put together in a vat, but, in fact, a very sophisticated molecule grown in living cells in facilities that are extraordinarily expensive to build and because, in fact, the amount of data that needs to be taken to the FDA to not only characterize a molecule, but to demonstrate that it is as equally safe and effective as the brand, the original pioneer drug, is probably going to be very expensive as well. It is very unlikely that we'll see the kinds of reductions in the biological sector from competitive similars, as we have in the pharmaceutical. Thank you.

ED HOWARD: Thank you very much, Jim. We turn finally to the people who have the biggest stake in the success of this enterprise, and that is the people who are hoping to be able to take these new biotechnology pharmaceuticals for the conditions that have been addressed. They face a dilemma of a different sort, of being worried, of course, about the cost if you're trying to pay that 25-percent co-insurance that Jamie was talking about on the one hand. On the other, particularly if you're concerned about

those with severe and life-threatening conditions who want to be able to get the very latest pipeline drugs, the very latest possible treatments. We have a perfect person to address that dilemma for us today, M. Carolina Hinestrosa, who is the executive vice president for programs and planning at the National Breast Cancer Coalition. She is also the cofounder of Nueva Vida, which is a support network for Latinas with cancer in the Washington Metropolitan Area. She is a member a former chair of the integration panel of the Department of Defense Breast Cancer Research Panel. She served on a number of national committees at the Cancer Institute, the IOM, the National Quality Forum and others. We're very pleased that you've been able to join us today.

M. CAROLINA HINESTROSA: Thank you very much. I am also a two-time breast cancer survivor and a mother of a 10-year-old daughter who I hope will never have to face this disease. Thank you very much for the invitation to participate in this panel. This is an issue of great importance to us at the National Breast Cancer Coalition, not only as the potential recipients of these types of interventions, but also we've taken the approach that we want to be there and we want to be driving and participating in the generation of these new and effective interventions in health care.

I want to tell you briefly about the National Breast Cancer Coalition and why we have an interest in this issue, not only from the consumer end as recipients, but also from the research part, and also our current thinking on this issue.

The National Breast Cancer Coalition is an advocacy organization. We have hundreds of member organizations and thousands of individual members. Our mission is to end breast cancer. We work on this from three approaches: research, access and influence. We spend a great deal of our resources educating our members so that we can participate in the research process, not only as subjects of research, but also to sit at the table with researchers and set priorities for research, as well as public policy. We developed a Clinical Trials Initiative early on, precisely because of this interest in improving the clinical trials process, ensuring that there's innovation and that we really have an active field so that options for women with breast cancer can improve, and also that we generate solid levels of evidence. So as part of the Clinical Trials Initiative, we have developed some partnerships and we created criteria for those partnerships to ensure that we would sit at the table, set priorities and that we would participate in particularly innovative clinical trials. Before I do this, the criteria that we set for participating and collaborating with sponsors

of research in clinical trials is it has to be an innovative approach in breast cancer, it has to be answering an important question, addressing a major gap in breast cancer, and there has to be opportunity for meaningful input and involvement of consumers, among other criteria, but I wanted to refer to those today.

So we set up these collaborations, we participated in data safety monitoring for the trials, we participated in the steering committees of these clinical trials and we work on outreach for the trials and education of the community for these trials. We expect that the company or the institution that is sponsoring the research will afford those meaningful opportunities to consumers on those trials. We also require that they commit to publish the results of the studies, whether they are positive or negative results or whether the drug was approved by the FDA or not.

The earliest example we have in this area is our collaboration with Genentech on the approval of Herceptin in the metastatic setting. Again, this was intriguing to us because it was a new approach in breast cancer. It targeted therapy, addressing a major gap in breast cancer, a type of breast cancer that was particularly aggressive and for which there were really not good options. Then the technology around it – it was a biological approach and looking at a monoclonal antibody to really target that pathway, the HER2

pathway. Also, the promise of this was that when these biologics was that there would be much less toxicity for people with cancer because of the very targeted approach. The outcome of this story many of you know. Herceptin was approved by the FDA. The company, Genentech, has publicly acknowledged that this drug was approved two years sooner because of the involvement of the National Breast Cancer Coalition the way that I described to you earlier. We helped the company also with a fair expanded access policy. When information was up there that this was an active agent, there were a lot of issues with access and we helped with that. Most importantly really, the outcomes of the trials looking at meaningful outcomes like survival in this indication. There was a lower death rate and longer survival. Still, the effects of this drug have been seen to be best when combined with chemotherapy, quite a bit of quite toxic chemotherapy, so there is toxicity still remaining, both because of the combination of chemotherapy and because of the drug itself. Also, the other downside of this is the very high price that we have to pay for this medication. So there are some very good things and some not so good things.

Now we're looking at the future and we have recent news of Avastin in breast cancer as well. There's some promising data in the metastatic setting. Now the future is looking at combining these biologics, Herceptin and Avastin,

and looking at whether we could bypass the chemotherapy path. But at what cost? The concern really is that the improvements in efficacy remain to be seen. The toxicity question – we don't know if it is going to be there. But what we can be certain about is that if we go this path, the prices are going to be much, much higher. Herceptin is about $40,000 a year. Avastin has been announced to be about $100,000 a year in breast cancer. Imagine the future. So we need to be looking very carefully at dose and duration and really have the right data, but also it is a great concern.

We, as an organization, are very, very concerned about the trends in oncology drug pricing, not only for patients, but also for the health care system. As has been said here, we have many millions – close to 50 million – people uninsured. The public sector is speaking more and more of those uninsured. There are tremendous disparities in coverage among those who are insured and there is an increasing shift onto consumers to pick up the burden.

In terms of the approaches that have been mentioned about what the public sector, private sector is doing to address this cost, we strongly believe that the FDA has a clear role, even though they don't make coverage decisions, in making sure that we have the robust evidence of the efficacy and safety of these agents. When FDA approval is granted, it will need to insure that sponsors of research

really complete the trials they committed to conduct, so that we really have robust evidence.

Also, we are supportive of the evidence-based approach that came out on the coverage under evidence development, but we need to be very, very careful on the quality of evidence that we are generating because, as we know, not all evidence is created equal.

In the private sector, clearly we are seeing that most of the pressure really to control cost is coming from the private sector and they are leading the way in this regard, but, unfortunately, we are also seeing an increased burden on consumers. The industry has announced a number of initiatives to help cover the costs. Almost all companies have a charity to help patients access their drugs. We believe this is really not a fix to the problem. It is an artificial fix, a bandage approach and we really need to do better than that. There is an issue that is a question in our minds. We don't see a rationale explanation for the price inflation in these agents.

We need to remember here that we are addressing essential human needs. All drugs that work should be addressing essential human needs. Our government has acknowledged this and has created incentives for innovation and to ensure access. We have patents, we have exclusive rights, we have tax benefits and we have, of course, a great

deal of research dollars that are put into health. The government has created that, so society expects a [inaudible] for more players in the system from industry, from providers, from consumers and from the government, especially when public resources are being utilized.

We are, as I said, for evidence-based health care in the rational use of resources by everyone, including consumers. However, in this marketplace, we have a great imbalance. We are talking about people who need certain products and, therefore, because of their need, their demand in inelastic. We also know that many consumers are sheltered in terms of the price they have to pay, so that makes that demand also less elastic. But also, consumers have very limited information on the efficacy and the side effects of these agents, and they are in a vulnerable situation where they are making decisions about consuming these resources. Consumers also rely on providers for decision-making. While we hear horror stories of consumers who go and demand that they receive a certain intervention or a certain drug, this doesn't happen in a vacuum. We know that a lot of this happens because of advertising. It also happens because of media reports that are hype. So we are all responsible here.

We are also puzzled by the changing argument, in terms of what justifies the price of these drugs. Is it the cost of production? Is it research and development? Is it

innovation? More recently we hear that it is value, that we are pricing these drugs this high because of the value they have. However, we cannot allow industry to solely determine the value that society must pay. In addition to the contributions that society has made already, in terms of, again, tax credits, research dollars, exclusive right, and also the altruism of people who participate in these clinical trials who are expecting they are doing to do better or contribute to the good of society. We also must remove incentives that allow providers to obtain financial gain on the basis of the price of the price of the drugs they administer. We must strive for transparency in the marketplace for pharmaceuticals so that consumers are educated about the known benefits and limitations of interventions and the financial consequences to themselves and the health care system of their choices – that is, if they have a choice.

We must develop a system approach to ensure that patients have access to the drug they need when they need them and that that system is sustainable. NBCC believes that we can simultaneously accomplish the goals of innovation and access, but our fear is that while it is unclear whether we need the prices at these levels to foster continued innovation, we can be certain that consumer access is going to be eroded.

ED HOWARD: All right, thank you very much, Carolina. We now are at the part of the program where you get a chance to ask your questions. You can fill out the green card and hold it up or you can go to one of the microphones. Let me just note in advance that both Lisa and Jamie are trying to catch planes to the West Coast. The joy of having people that are not necessarily from right around Washington is counterbalanced by their need to make a plane at Dulles, which isn't as easy as it may be from other places. They're going to have to take their leave probably before we finish with the Q&A. That may give you a clue as to whom you should want to direct your initial questions to anyway.

I'd like to start off as we're waiting for you to get your questions organized. It was triggered by something Jim Greenwood said about the possibility that it would be very difficult for a generic equivalent for many of these biotechnology compounds to be approved and, if some, at some significant price advantage. I wonder what Jamie and Sean might have to say about that. Is that something that you can foresee, and what is the extent of the barriers that Jim referred to?

SEAN TUNIS, MD: While this is certainly not an area of expertise about the generic biologics, but I've heard

enough about it. I think, following Jim's comments, that because of the complexity of these compounds, the notion of generics doesn't have the same application that it does with small molecule. I am not confident that we're going to have the same opportunities for price competition amongst generics and patent-protected products that work in the small molecule space. Obviously, there is lots of interest on the Hill in figuring out a way to do this and a lot of activity about it. I just think that sort of on the scientific level, it's going to be a challenge.

ED HOWARD: Jamie?

JAMES C. ROBINSON: I would agree with that, but I would add that it's a little bit of a self-fulfilling prophecy because in order to have biosimilars or follow-ons, you need to have a regulatory pathway that would allow them to be processed by the FDA. But such a thing does exist in Europe and in the European Union, there are a certain number of follow-on biologics that have been approved and that are getting to the market there. But such a regulatory pathway does not exist in the United States, in large part because of the industry opposition. There is a science dimension to this. There is also a political, regulatory dimension. I would say, let's set up a regulatory pathway and if the

science is so difficult that there are no candidates, well, so be it. But that is not a reason to not have a regulatory pathway in those instances where it would work.

ED HOWARD: Okay. Oh, yes. If you would, go to the microphone. If you would, identify yourself and if you want to direct it to one of the panelist, please do so.

ROLPH ROSENKRANZ: Rolf Rosenkranz with *Inside CMS*. I have a question for Mr. Greenwood and maybe also for everyone on the panel. This is piggybacking on what some people have already said today. I'm wondering what now, from creed strategies, generic makers would be more structural, maybe policy-related strategies to push their product. As we've heard today, comparative effectiveness studies are not being undertaken on a grand scale. ARC is just doing some. Maybe they're not even wanted by bio companies. Then we have national coverage determinations, which might not be so popular among drug makers today. Also, I'm kind of wondering, is it even a strategy, for instance, for bio companies to maybe eradicate utilization management tools that a lot of plans – for instance, in Medicare – have right now on those bio products? If so, I'm sure providers and plans would probably caution against that, too. So what are

some maybe more structural, policy-related strategies that you are following?

JIM GREENWOOD: I'm not sure that I caught all that, so if you could go back to the microphone and just give me the first piece of that. You raised about three or four questions.

ROLPH ROSENKRANZ: Right. I'm just trying to understand how you're trying to increase access to biologic products. Apart from educating providers about them, there must be some more structural strategies that are more related to policy, payment policy to Medicare policy.

JIM GREENWOOD: In terms of how we're trying to expand access, let me give you a microscopic level and a macroscopic level. First of all, the microscopic level. I have spent time visiting, for instance, HIV/AIDS clinics in Washington, D.C. to make sure that access to our products is not an issue and to make sure that our companies are prepared to donate. Our companies donate a vast amount of products to clinics and to other individuals who cannot otherwise find coverage. For instance, if you take Genzyme's product, which is one of the most expensive at $150,000 for Gaucher's disease, they basically have two prices around the world.

One is $150,000 if you have insurance coverage, and the other is $0. So I would say that. I would also say that there has been a lot of legislating around the access issue, which unfortunately has gone consistently to a stalemate in the Congress. There have been proposals for associated health plans, for instance, and other mechanisms that would enable people to join together without certain anti-trust violations in order to access health care less expensively. Unfortunately, the partisanship in the Congress, of late, has prevented those kinds of approaches from being enacted.

ED HOWARD: Yes, in the back, please?

MERRILL GOOSNER: I think this is for Dr. Tunis. I'm Merrill Goosner with the Center for Science in the Public Interest. In this very issue of *Health Affairs*, there is a discussion about CMS' attempt to use evidence-based medicine around payment for end-stage renal disease, specifically Amgen's product Epogen. You are very familiar with those efforts and what the article in *Health Affairs* suggests, of course, is that the actual health care outcomes, as a result of CMS' policy, have actually turned negative and may actually be harming some patients. So my question to you really is this: This is a case where there was some evidence and either it was applied improperly, or perhaps the quality

of evidence that was available to CMS wasn't accurate. There may have been other forces at play that you were aware of. What accounts for a kind of failure to use evidence in what would appear to be a medically proper fashion?

SEAN TUNIS, MD: I think one of things I learned from a few years of trying to do clinical policy through coverage and payment at CMS is that they are inevitably imprecise tools and often don't account for unintended consequences, particularly of other financial incentives and restraints. So without going into the specifics of what went wrong there, I think that there are all kinds of considerations that patients and clinicians take into account – in terms of clinical decision making – as you know, and only one of those has to do with the coverage and reimbursement policies of Medicare or any other payer. I just think that the direction that I think the private sector is going – and I think that Medicare will probably follow – instead of trying to precisely impose clinical decision making through coverage or reimbursement policy, the policies will be structured to try to give that information to patients and clinicians, align the financial incentives properly, and then those decision-makers will need to do the best that they're able to do. I can think of five other examples, or more, where the intention, particularly of a coverage policy, was to achieve

a particular clinical practice outcome and for reasons that we didn't anticipate when we developed the policy. The pattern of care wasn't consistent.

ED HOWARD: Jamie, you talked about private sector efforts to control costs and assure appropriate access. Are you satisfied with the quality of the evidence that private payers are using to make those kinds of steps?

JAMES C. ROBINSON: The question is, what is the quality of the evidence that the private insurers use to do anything in this domain? Of course, the evidence is terrible. First of all, there is the basic science – we don't understand the basic science. Then, as Sean pointed out, there is a variety of data gaps in the kinds of clinical trials. Thirdly, the private insurers tend to be disadvantaged – compared, for example, to Medicare and CMS – in their ability, their staffing, to cogitate all this because simply the economy is a scale and having the best and the brightest scientists – how many oncologists do you have at your disposal, so to speak, in evaluating a drug? Smaller health plans, in particular, have fewer. Then, of course, there are cultural matters. But if we look at who is better at this – if you want to think of it in a really crude sense – who is better at doing this kind of coverage policy, CMS or

the private insurers? That's sometimes an interesting question. I would say it is a tradeoff. I think that CMS has better science, better people that can work on that. They're bigger, they have more clout, et cetera, but they are a big target under relentless, very sophisticated lobbying. You don't even have to look at biologics. You just have to look at where they try to revise DRGs. The medical device industry is very sophisticated about dealing with CMS. Private insurers are not lobbyable [misspelled?] in that direct sense and, plus, there are lots of them. They're scattered around and they're murky. On the other hand, they're less sophisticated, they have less scale, and it is it a little more of a seat-of-pants type flying and they're more likely to make a mistake, to deny something that should be covered or something like that.

ED HOWARD: Yes, Ray?

RAY WARRENSTON: Yes, Ray Warrenston [misspelled?]. I do some consulting in the benefit plan area with employers back in the Midwest. Sean, you mentioned – and I think this is a really good point – that decision-makers have no significant role in the creation of evidence. I would assume you're meaning more in the dissemination of evidence, than in the actual creation of evidence, or am I wrong?

SEAN TUNIS, MD: No, I mean in the actual creation of it. I mean everything from picking which questions would be actually studied, setting the priorities, as well as actually the design of eligibility and exclusion and inclusion criteria, which outcomes, the length of the study and all those things, which are generally designed from kind of a scientific point of view of what would be nice to know to sort of understand this without adequate consideration of what do the people who are going to use this information need to know to make the kinds of decisions they need to make?

RAY WARRENSTON: I wanted to do a quick follow-up on that. As someone who has worked for a long time with the definition of medical necessity, which is, in my opinion, kind of a barrier to the movement of innovation. A lot of it is based on notions of if you're paying for care, which is where the rules come from, you want to be concerned about overuse, underuse and misuse – those characteristics of poor quality. What we're trying to do – this is a question really – is how or is there anything going on to bring consumers into the decision-making process, into the development of what I would call more elastic approaches towards coverage. I'm thinking of the Chats [misspelled?] movement, and I'm thinking of the work that Sacramento Healthcare Decisions has

done to say that consumers are very resistant to cost effectiveness criteria in benefit decision making. The point is, is there a way to bring consumers into this process, not as simply demanders of the latest and the best, but as more realistic adopters of innovation, based both on cost and whatever evidence is out there? I hope that is an understandable question because it is something I'm working on.

SEAN TUNIS, MD: Yeah, well, maybe, Lisa, you want to talk about your efforts to do this with the California Technology Assessment Forum? I think that has been a priority for you all for several years.

LISA PAYNE SIMON: Yes, thank you, Sean. Our California Technology Assessment Forum is a group of experts that review new and emerging technologies – about a dozen a year – and on that panel we have medical experts, clinical experts and also an ethicist and a consumer representative. So that is one way in which the consumer perspective is embedded into the process. She is a very active panel member. The other thought I have, in terms of work that's going on in California – to punt it back to Sean [laughter] – is the Center for Medical Technology Policy is planning on doing some work along the lines of patient/clinician advisory

committee. Sean, would you like to say something about that? That strikes me as something relevant to this area.

SEAN TUNIS, MD: Right. Just quickly on that – The Center for Medical Technology and Policy is really about trying to develop the kind of evidence I talked about that was missing. Our whole organizational structure is built around the information needs of patients and clinicians. Sort of the senior advisory body for the Center is composed of a majority of members that are patients and clinicians. The idea being that those are the decision-makers for whom we really want to try to develop a better infrastructure for producing information. I do think that – and Carolina would have a good sense of this – they've been very successful in terms of having patient and consumer representation in the arena of clinical research, particularly NIH. But in my efforts on Medicare to bring more patient representatives into coverage decision making, it would always seem as though we had one or two people oftentimes not fully able to follow the technical nature of the discussion. I think generally pretty suboptimal in terms of really incorporating patient perspectives into what we were doing.

M. CAROLINA HINESTROSA: I think the answer to the question is yes, there are ways to do it, and it can be done

right. As Sean mentioned, the National Breast Cancer Coalition has created a model of consumer involvement that really is based, first of all, educating the consumers on the issues and on the language of science and really the concepts that are critical, not the latest in breast cancer. Actually, someone said that the consumers want the latest that is developed. We really teach people to be educated consumers of health care. We have created a very successful model in the research world with the Department of Defense Breast Cancer Research Program where consumers participate in peer review of the proposals – and we train them to take that role – but also in setting priorities for the program, in setting a vision for the program, in developing mechanisms that the scientific community can utilize to then do innovative research. The major emphasis of that program in on innovation and on creating mechanisms that scientists can use to produce innovative research. So that is in the research arena.

In the health care arena, of course we can do it. We have also created a training program on quality care for consumers. Sometimes in the area of research, the place that people go to obtain funding for innovative ideas that are not constrained by the existing parameters and sort of the existing rules is the Department of Defense Research Program. It is a place where you can take risks and you can generate

new ideas. In fact, the critical funding for the initial studies on the HER2 pathway were funded by the DOD program. NIH didn't believe in the story and they didn't want to take the risk. So this is all consumers playing a critical role in pushing the scientific community to do things a little bit differently and still stay within the relevance of their research.

ED HOWARD: Okay, yes. Go ahead.

JERRY STUFFELL: Jerry Stuffell [misspelled?] with WellPoint. This question is for Chairman Greenwood. What insight can you provide on BIO's position regarding the creation of a pathway for follow-on biologics, either through Hatch-Waxman or the Public Health Service Act?

JIM GREENWOOD: Did you say, what is our position on that?

JERRY STUFFELL: Yeah, or what insight can you provide on your position?

JIM GREENWOOD: Well, I spent a fair amount of time this week and I will spend a fair amount of time next week talking to members of Congress about follow-on biologics.

One of the things I'm attempting to do just as a precursor to the discussion, which is certainly going to happen in the Congress next session, is I take with me a plastic model of an aspirin molecule and I take with me a DVD player with the image of an EPO molecule. I demonstrate the difference in size and complexity between a chemical compound and a protein that's been developed in living cells. I begin to explain how relatively simple it is to characterize one based on a very straightforward chemical formula, as opposed to characterizing a very large-molecule biological that is vastly more complicated, has various kinds of folds and structures and may have bicosillated [misspelled?] structures to it as well. Just to begin to explain that it is very, very difficult to characterize these large molecules and that it is important for safety's sake that if a pathway is to be created for follow-on biologicals, that the sponsors of those applications bring to the FDA a complete set of clinical data that demonstrates that, in fact, that molecule can be just as safe and be just as effective. We think that that requires clinical trials in order to make that case sufficiently to the FDA. Obviously, there are differences in molecules. Human growth hormone is not the same as EPO.

ED HOWARD: Can I just follow up a little bit? We heard some discussion of some European countries having

mechanisms that do precisely what you're talking about. Are you in a position to comment one way or another about whether those are reasonable regulatory pathways, or are they applicable in comparing the situation in the United States?

JIM GREENWOOD: I don't claim great expertise on that. I believe that they're in fairly beginning stages of that process with relatively uncomplicated molecules. I believe it is also the case that they don't allow for these so-called generic substitutions, but they require that if there is a follow-on biological that it be prescribed on its own, as opposed to being substituted at the doctor's office or the pharmacy.

ED HOWARD: Yes, sir?

TATE HEUER: Tate Heuer with Senator Pryor's office. Going back to the issue of generics and competition verus innovation, on the pharmaceutical front, we've seen studies where the U.S. prices of drugs were compared to foreign prices of drugs. A lot of the pharmaceutical company spokespersons have responded to that and said, "Yes, but we have much more vigorous generic competition in the U.S., so when you look at drug spending as a whole, it may not be as great." Also, looking at what we've been talking about, the

European and generic competition, I understand the concerns you have about it being hard to have a model or a pathway and it could be more expensive and not competitive. But also, when we revisited Hatch-Waxman and our generic drug approval system here in 1984, there was a general agreement and a consensus that having a reasonable period of patent protection and market exclusivity also encouraged innovation and that if a drug company knew their patent was going to run out, than there was a race and an urgency to getting a better drug and to have that drug on the market. We have benefitting both from that and from lower prices from generic competition. If that doesn't pan out in the biological marketplace, what kinds of other forces do you see that could lower prices for products that have been out for a while and encourage the innovation of new products?

SEAN TUNIS, MD: Just to be clear on the follow-on question, I don't view it as a political question. It's a scientific question. It's not a question of lobbying for or against policy, so much as it is answering some very important, sophisticated scientific questions about how much data needs to be presented to the FDA before equivalent safety and efficacy can be claimed. I wanted to be clear about that.

On the question of what I think will bring down the price of these drugs, first of all, if I go back to my very first comment, which is let's make sure that we're thinking about the net cost because a drug that costs $25,000 and prevents $100,000 in surgical and hospitalization costs is not a coster [misspelled?] to the health care system. Across the board, I think a very strong can and has been made that pharmaceutical products are preventative. If you look at the cost of Lipitor and compare that to the cost of heart disease, coronary disease, from cholesterol, I think the facts are pretty clear. I think, frankly, the technological advances in the way these drugs are produced will bring down costs. I think perhaps technological advances may enable us to do smaller, more precise clinical trials and that may bring down the price. So much of the cost is in the clinical trial phase, so I think technologically we can reduce the cost of clinical trials and the cost of manufacturing.

M. CAROLINA HINESTROSA: I'm glad that you're mentioning the age of technological advances and sort of giving us some promise there. I'm glad to hear you say it because the health care industry is the industry where we have actually seen that technology has driven the costs up and not down. So I would hope that they release a commitment from industry to really making that happen, that technology

is going to get us more value for money and get better outcomes at a lower cost. But so far, the data doesn't go that way.

JIM GREENWOOD: I understand that, but I also think that we need to understand where we are in the history of this technology with the advent of the history of biotechnology. As I said, when we were at the advent of telecommunications technology, it was extraordinarily expensive. When we were at the advent of computing technology, it was extraordinarily expensive. Technological advances, so long as they have not been hampered by insufficient revenue to continue to innovate, have been what have consistently brought down costs over time in technology after technology.

ED HOWARD: If I can ask you to be patient for just one more minute, there is a question on a card which I would like to get into the discussion, at the risk of seeming to pile on, if you will. The questioner says, "Why are these drugs so expensive? Does it have anything to collusion, tacit or otherwise?" I say that which is not based on science.

JIM GREENWOOD: We're not oil industry. [Laughter] No aspersions to by brethren in the oil industry. [Laughter] But let me try to answer the question as to why these drugs are expensive, because this is very important for us all to understand. Let me give a brief history of a biological.

Somewhere in a university someone – after many, many years of research – has begun to discover that a disease is caused because a gene in the patient is failing to cause to be produced a protein that is necessary to avoid that disease state. That research enables that team of researchers to begin to think, "Well, you know, we could perhaps bioengineer some cells so that they could produce that protein, and then we could inject that protein into the patient, thereby producing a cure or a treatment." The folks who get to the point where they think they can actually go out and do this will sometimes leave the university and they'll look for angel investors. The angel investors might invest a few hundred thousand dollars to see if they can get to some kind of proof of concept of what they are doing. If they are fortunate enough to succeed in their endeavor – and they usually don't – then they'll build a scientific team. It tends to be expensive to get a bunch of really smart PhDs and all of the expensive equipment they need to continue the process. Eventually, they'll turn to the venture capital community and they'll borrow millions of dollars – 10, 15,

20, 25 million dollars – from the venture capital community so they can begin to gear up to actually produce this product. The burn rate for these companies is extraordinary. If they are fortunate enough, they'll get to a clinical trial phase where they have to pay for the treatment and for the physicians to treat sometimes thousands and thousands of patients over many years. That is extraordinarily expensive. That can cost hundred of million of dollars and taken 10, 12 years or longer. They'll then go build a facility that might cost $0.5 billion dollars, or they'll do something like grown trillions of Chinese hamster ovary cells bioengineered to produce this protein with these extraordinary requirements for purity and so forth and quality control. After spending that billion dollars plus, maybe going public, they'll maybe get FDA approval, but probably not. They'll probably have to go back to the drawing boards and try something else. But if they do get FDA approval, then they can hire a marketing team and begin to make their first dollar of revenue, which may take them the entire life of the patent to recoup what they've sunk into the cost so far, let along have extra dollars to innovate the next project. So that is why they are so expensive. No, it has nothing to do with collusion.

MALE SPEAKER: All of that is true, actually, and I wouldn't dispute any of that, although I think there is

another fundamental reason that at least probably goes along at the same time with that. Jamie is here. He is a registered economist and he can tell me if this is right or wrong. I would call this partly the Weston effect – the Weston being the Weston Hotel – which sort of answers the question of why does an egg for breakfast cost nine dollars at a Weston Hotel? I think part of the reason is that most people are there on an expense account, so they're not really that price sensitive when it comes to what they're spending for breakfast. Most people don't want to walk down the street and get a normal two-dollar egg. I think partly it's the Weston effect. It's priced because the structure of our health care system is such that that's what will be paid for them. I don't think that biotechnology companies or the pharmaceutical industry have any obligation to lower the prices, to sell something for a lower price than they can get. I think this is where the issue comes in of what kind of mechanisms are the payers and others doing to sort of bring some price sensitivity into the system? At the end of the day, I still think it is exactly those prices that feed back into investors being willing to give the hundreds of millions of dollars. But I don't think that that by itself is what then explains the fact of what the high price is.

JIM GREENWOOD: I would also say that it's the difference between a nine-dollar egg that cures cancer and a two-dollar egg that doesn't. [Laughter] I would also say that if we're not willing to pay $9 dollars for the egg that cures cancer, we're not going to cure cancer.

M. CAROLINA HINESTROSA: Just if I might say, we have not cured cancer. We have some promising data, but we cannot say we have cured cancer.

JIM GREENWOOD: This is called the promise of biotechnology.

MISSY JENKINS: My name is Missy Jenkins, and I'm with the Pharmaceutical Care Management Association. We represent the payers, with the PBMs and representing the payers. I want to follow up on two things that you said about clinical trials, because I think probably, in the end, if you look at developing a pathway, the argument is probably going to center around clinical trials. On the one hand, you said it would reduce costs if the innovator companies were not required to do such extensive clinical trials. On the other hand, you said that it would be BIO's position that the follow-on company be required to do extensive clinical trials. I'm just trying to figure out if BIO's position is

that more clinical trials are needed for the follow-on company than for the innovator company?

JIM GREENWOOD: Oh, no. It's certainly not our position that more clinical trials would be needed for the follow-on than for the originator, but we would certainly argue that in most instances you would need as much clinical data brought with the application as you did with the originator because the process is so vastly more complicated than with a simply, small-molecule chemical.

ED HOWARD: Here's one that resonates with those of us who have been around for a while. "Since the discontinuation of the Office of Technology Assessment, such assessment is now done very inefficiently in this country; some might say not much at all. What is the panel's view or views on whether an oversight group will again be created – whether governmental or otherwise – and funded…" The question says, "…for all or even for a substantial amount of the work that should be done?"

SEAN TUNIS, MD: I was actually the director of the health program at OTA when it was shut down, so I've been lobbying for years to bring it back. This question comes up in the form of is it likely that something like the OTA or

something like the US version of the National Institute of Clinical Excellence (NICE) in the UK would come of that. It would be a sort of centralized function for looking at risks, benefits and cost effectiveness of new technologies. My personal view is I don't see that becoming a government function. I think if you look at the history of bodies of technology assessment in the U.S., that's an awfully risky business. They don't last for very long. I think that it is pretty nicely that one would be reestablished. What I think it is an interesting possibility – for some of the reasons that I've sort of articulated – that there may well be some kind of public/private collaborative initiative to central some of the technology assessments, systematic review, priority-setting functions that would be jointly funded by payers and others. So I think there is a growing recognition that for every payer to have their own technology assessment organization, for there to be a bunch of small entities that do this and review the same evidence – Cochran Collaboration reviews that same evidence – is pretty inefficient. I think the likelihood of some kind of centralized function, but non-governmental is pretty high.

JIM GREENWOOD: When I first got to Congress, when Republicans were trying to balance the budget, I was persuaded to vote to close the office by a great member who

was on the board of the office. Anyway, he persuaded me to change my vote and I voted to save it, but it went away anyway. I just can't imagine, given where the federal deficits are right now, that Congress is going to be rushing to create new entities.

M. CAROLINA HINESTROSA: I would say that we absolutely need an entity of that kind. Clearly, we cannot have the same format we had before because it would be incredibly vulnerable, but there is an important role in that in creating more efficiency in the system. That is one place where robust consumer representation would be very helpful.

ED HOWARD: If I can just summarize that you just heard – there are two separate questions or threads to the answer to that question. One is whether you need it and whether there is money enough to fund it. The other is where it sits. Do we trust government enough to set it up again, whether it's attached to the Congress or to the Executive Branch? Do we trust the payers, who have a vested interest in something less than maximum spending, to fund something like this? It is a very delicate and, it seems to me, very complicated process to try to come to the rebirth of an entity like this with enough resources to really do some of this stuff. That's personal opinion.

We have come – unless you want to go back to the microphone – to the end of our time. One last question.

MALE SPEAKER: Several points addressed the question of the scientific side of biogenerics, so let me ask a question about the cost side. I've looked at a number of the profitable biotechnology balance sheets, and their cost of goods sold as a ratio of their overall balance sheet is not different than a traditional pharmaceutical company. In other words, the profits take so much, R&D takes so much, administration and sales takes so much, and then cost of goods sold. It is generally a fairly small fraction – somewhere between 5- and 15-percent. In your remarks, Chairman Greenwood, you said that it was not just, not having a pathway in the scientific question, but also a cost question. Wouldn't it be true that if there was a scientific way to get out a biogeneric in a regulatory pathway, that the same level of savings would be achieved, in terms of a generic firm entering the business, simply because most of those other costs would be eliminated?

JIM GREENWOOD: I certainly wouldn't argue that there would be no savings. I would argue that I've seen studies – and I don't have them with me – that would indicate that the savings wouldn't be anywhere near as dramatic. Again, it is

because in the generics small-molecule world, you have virtually no clinical trials to pay for. What, in fact, the FDA seems to be saying is that it would need significant clinical trial data, since you otherwise readily characterize the molecule. The follow-on companies would have to make substantial investments in clinical trials, which are expensive, and make substantial investments in manufacturing because the manufacturing technology is very, very complex and is proprietary. Given the complexity of that, I think it is a reasonable question to ask how much competition would there really be? Because of the sophistication of the process, would there be as many companies rushing in to participate in a competitive follow-market as there have been in the small molecules? My reading of the studies is that there probably would not be. It's hard to predict.

ED HOWARD: All right, that is the last substantive word. It's not the last word. I always reserve that for myself. I want to thank *Health Affairs* and Lisa Payne-Simon and her organization for helping us get this event together with such a luminary group of participants. Thank you first for filling out your evaluation forms, which I know you're all doing right now, and for contributing to what I think was a very rich discussion. Most importantly, I'd ask that you

join me in thanking our panel for an incredibly good

discussion on a very complicated subject.

[Applause]

[END RECORDING]