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FEDERAL TRADE COMMISSION

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FEDERAL TRADE COMMISSION

IN RE:)
ROUNDTABLE ON THE ECONOMICS)
OF THE PHARMACEUTICAL) File No.
INDUSTRY) P065800
)
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FRIDAY, OCTOBER 20, 2006

Federal Trade Commission
601 New Jersey Avenue, N.W.
Washington, D.C. 20580

The above-entitled workshop commenced,
pursuant to notice, at 9:00 a.m., reported by Debra L.
Maheux.

1 P R O C E E D I N G S

2 MS. IPPOLITO: If we could get started. Let's
3 get going because we're almost on time, and I'll leave
4 it in good hands. It's my great pleasure to welcome you
5 today to the FTC.

6 (Discussion off the record.)

7 MS. IPPOLITO: Well, thank you very much for
8 being here. I would like to welcome you to the FTC.
9 This is a Roundtable on the Economics of the
10 Pharmaceutical Industry.

11 As I'm sure you know, this is a very important
12 market for us. The Federal Trade Commission has the
13 primary antitrust responsibility for pharmaceuticals,
14 and so in that capacity, we review most mergers in the
15 area. We review lots of contracts between branded
16 products and generic products and other kinds of issues
17 like that, and we look at how firms interact with the
18 regulatory apparatus and occasionally pursue matters
19 there.

20 So it's been a very active area for us and one
21 where we're spending quite a few resources, so we want
22 to make sure that we have as good an understanding as we
23 can of the industry.

24 In addition, the FTC has primary federal
25 responsibility for advertising, not pharmaceutical

1 advertising it turns out. FDA has that, but because of
2 our interest in advertising, we're following the DTC
3 experiment, experience very closely to see what we could
4 learn from that whole episode: What does advertising
5 do; how much does it spread information, spur
6 competition, or is it all about raising cost?

7 So it's an area that we track very closely, and
8 I'm happy that we're going to have a panel on that as
9 well today, so I don't want to take a lot of time so we
10 can get to interesting things, but before we get
11 started, I did want to take a minute to thank Chris
12 Adams who put this together and did a terrific job of
13 getting together very interesting panels for us and very
14 good speakers, and also say a word to our staff, who
15 always -- these things are not as easy to put on as you
16 would think, and so especially Van Brantner and Tammy
17 John, who handled all the logistics for us.

18 So with that let's get started. I have the
19 great pleasure of introducing Ernie Berndt, an economist
20 who probably needs no introduction in this kind of
21 audience. Ernie is the Louis B. Seley professor of
22 applied economics at MIT Sloan School. Ernie has been
23 involved in economic research of healthcare issues for
24 as long as I can remember, and that's a long time, so he
25 will give us the benefit of his wisdom by beginning with

1 an introduction to the economics of pharmaceuticals.

2 MR. BERNDT: Thank you. While I try and get
3 this cursor to move up, let's just say it's an honor and
4 a pleasure to be here.

5 In thinking about what focus would be
6 appropriate for my opening remarks, I thought it useful
7 if I begin by reminding ourselves that biotechnology and
8 pharmaceutical firms are components of a larger
9 healthcare products and services sector, and that as
10 such, they share a set of characteristics and attributes
11 that differentiate them from non healthcare industries.

12 I want to go a bit further than that this
13 morning in my opening remarks, and rather than just
14 reminding you of the biotechnology and pharma DNA in
15 healthcare, I want to ask ourselves the following sorts
16 of questions: In comparison with other healthcare
17 product and service industries, what features and
18 characteristics of the U.S. biopharmaceutical industry
19 are essentially the same, are different in intensity but
20 not in kind, and are very distinctly different?

21 I'm going to lump together for the most part
22 this morning the biotechnology and pharmaceutical firms
23 and industries. They are different in some important
24 ways, but in many ways, they're common as well, and
25 where they differ and have significant economic

1 implication, I'll make a point of commenting on that.

2 Then having identified ways in which industries
3 are the same as, slightly different from and very
4 different from other healthcare industries, I want to
5 ask: What are the implications of these similarities
6 and differences for understanding current issues and
7 controversy? In a sense, this presentation builds on a
8 discussion in the opening chapter that Roy Levy had
9 several years ago when he did the FTC study on the
10 pharmaceutical industry, and this will, I hope, update
11 that as well a bit, so let's start out with the two
12 biggies: In what way are the pharmaceutical or
13 biopharmaceutical industries similar to other healthcare
14 industries?

15 The two big biggies, very big biggies, if you
16 will are: Are healthcare costs for pharmaceuticals are
17 rising more rapidly than the CPI? This is very common
18 for healthcare costs in general. While it's very
19 challenging and difficult to measure price changes for
20 healthcare products and services, particularly holding
21 quality fixed, the general perception right now is that
22 at least as viewed from the PPI or the producer price
23 index, while pharmaceutical costs are rising more
24 rapidly than the rate of inflation overall, that not as
25 rapidly as hospital costs and probably more rapidly than

1 physician and dental cost, but to the extent that
2 pharmaceutical costs are sharing in this increase in
3 healthcare costs in general, they receive a lot of
4 public scrutiny.

5 A second reason or a second way in which
6 biopharmaceutical industry has a common heritage or
7 shares common issues with other healthcare industries is
8 that while healthcare costs and pharmaceutical costs are
9 rising in almost all countries globally, there's a
10 peculiar American issue, and that in this country we
11 have not yet decided, I'm not sure we ever will, on
12 whether access to healthcare is an entitlement or is
13 based on consumer's ability to pay. This raises all
14 sorts of additional equity issues, and politically
15 economy issues that complicate the pharmaceutical
16 industry as well as other healthcare industries.

17 From an economics point of view, what really is
18 an important distinguishing feature from healthcare
19 industries from other industries is the role of
20 information, and I want to make two comments about
21 information.

22 First of all, for most healthcare industries,
23 information is incomplete. That is to say the evidence
24 base is quite weak. It's very difficult to reliably
25 measure quality and compare quality and therefore to

1 compete on price given quality.

2 It's particularly weak in the area of
3 comparative therapies. We don't have consumer reports,
4 if you will, for healthcare services and products in
5 part because it would be prohibitively expensive, at
6 least I believe, to run those comparative trials.

7 So we have incomplete information in all the
8 healthcare industries, but worse yet, and I don't want
9 to -- not only is it incomplete but it's a symmetric
10 that is to say physicians are viewed as having better
11 information than consumers on certain aspects or at
12 least of care, but on the other hand, consumers are
13 aware of their own health conditions and to the extent
14 that insurance coverage is not universal or is not
15 mandatory, consumers have the ability to select into
16 insurance plans, and this creates dynamics for insurance
17 coverage that are quite peculiar to healthcare, but for
18 which biopharmaceutical industry shares a common set of
19 characteristics.

20 Finally, to make information even a bit more
21 asymmetric, if you will, professional journals have a
22 publication bias which tends -- it's been well
23 documented, which basically publishes results in more
24 successful projects being written up rather than failed
25 therapies or failed clinical trials, and to this -- and

1 it's commonly believed that as a result, we aren't as
2 fully aware of -- we don't have as complete information
3 as we might.

4 Those are the four most important broad
5 similarities with other healthcare industries. Let me
6 mention six others very briefly. Let me start with the
7 second one. Like the other healthcare industries that
8 have insurance coverage, so does biopharmaceuticals.
9 What that means is that at the margin we have something
10 called moral hazard, and by moral hazard I don't mean to
11 be talking about values or things like that. What I'm
12 talking about is that at the margin, a typical consumer
13 will pay less than the full social cost. Thereby
14 inducing what's called excess demand, so -- I want to
15 get back to that in a minute.

16 Other characteristics which the
17 biopharmaceutical industry shares with other healthcare
18 industry are the enforcement of patient privacy
19 protection, government being the largest single
20 purchaser, particularly now since Medicare Part D for
21 prescription drugs. As I mentioned, limited price
22 competition, in part because information is limited, and
23 limited pricing transparency with differentiated
24 pricing. The pharmaceutical industry often is pointed
25 out as an industry in which pricing transparency is not

1 very present but I think that's a common thing in all
2 healthcare industries. We don't know much about pricing
3 arrangements with various payors and even physician
4 payment mechanisms in the private sector.

5 So there's a lot of non price rivalry quality
6 that gets transformed into information that's
7 advertised, and I might just add that direct to consumer
8 advertising is permitted for pharmaceutical, but that's
9 common across the healthcare system.

10 Pauline Ippolito's written over the years a lot
11 about advertising information and healthcare. We've had
12 it since eyeglasses in the 1950s, hospitals can
13 advertise, and under a recent legislation, so can
14 medical devices now, not just pharmaceuticals, so that's
15 a rather common thing.

16 Okay. Those are the common characteristics with
17 other healthcare industries. Let's take a quick look at
18 some of the differences, differences in degree rather
19 than in kind.

20 The first one I want to point out is that patent
21 protection I think is considerably more important than
22 the pharmaceutical and device industries than it is in,
23 for example, surgeries. It's very difficult to enforce
24 a patent on a new surgical technique unless of course
25 you can take that surgical technique, bundle it with a

1 new piece of equipment, and then sell it as a device.
2 That's a possible way, but for the most part, the
3 pharmaceutical industry relies more for its economical
4 viability on patent protection than do the other
5 healthcare service industries.

6 Let me just make one digression here briefly.
7 When we all took economics 101 many years ago, we were
8 taught that monopoly power is bad because what monopoly
9 power does in patent protection, an example of it, is it
10 reduces quantity and increases price. Okay?

11 Now, when we have moral hazard, it is well that
12 then goes in the other direction, that is to say, you
13 now have moral hazard, which increases demand, not --
14 and offsets the reduction in static efficiency due to
15 patent protection. There's a very well written paper
16 recently put out by Allen Garber, Paul Romar and I
17 forgot who the third author is, that simulates variety
18 of utility functional forms and so on. It basically
19 shows that the two effects, moral hazard and reduction
20 in consumer welfare from patent exclusivity basically
21 offset each other, in that the social quantity may not
22 be the -- the actual quantity may not be that far off
23 from the socially optimal, although the price is much
24 higher because of both exclusivity and insurance.

25 Like other healthcare industry product industry

1 is regulated by the FDA, but probably more important in
2 this industry than in other healthcare industries.
3 Promotional activity is also regulated by the FDA.

4 Information is electronically available and
5 official practice behavior, both for commercial
6 purposes, but also for public health and research
7 purposes.

8 For example, it's important to know who it is
9 that continues to prescribe drugs after black box
10 warnings are issued and getting access to that type of
11 information can be very important for public health
12 purposes, not just for commercial purposes.

13 Relative to let's say hospital care or physician
14 payments, pharmaceuticals tend to have a larger out of
15 pocket co payment share, so in that sense they're
16 somewhat different. And finally, while there's always
17 been ambiguity in healthcare about who is a consumer, I
18 think for pharmaceutical, this complicity is much
19 more -- much stronger.

20 When they teach a healthcare course at MIT, I
21 always talk about the six Ps in pharmaceuticals
22 transaction complicity. As with other healthcare,
23 you've got the patient. You've got the physician who is
24 a learned intermediary and together with the patient
25 makes decisions about treatment. You've also got the

1 payer involved that has some constraints on the
2 physician, but when you get to the pharmaceutical
3 industry, you also introduce other players. You
4 introduce the pharmacist, and the pharmacist will work
5 together with the payor to determine what's on the
6 formulary, what can be prescribed, what cannot be
7 prescribed, what adverse interactions there may be.

8 You've also got pharmaceutical benefit manager
9 firms, PBMs, and now there's sort of -- they're analog
10 for physician administered drugs called speciality
11 pharmaceutical firms that also now negotiate directly
12 with payors, obtain different prices, and rebates get
13 involved and it gets to be quite complicated, and
14 finally you have public policy, which is while it
15 operates in the entire healthcare sector through
16 licensing and credentialing and so on, in
17 pharmaceutical, it's even more important, both because
18 of brand generic issues but also because of now our
19 Medicaid system as well.

20 So let me now turn to unusual factors or quite
21 distinguishing factors of the biopharmaceutical
22 industry, and I think there are three sets of conditions
23 which really distinguish this industry from most others.
24 The first one is conditions for entry. There's a long,
25 risky and costly product development process. It takes

1 much longer typically to bring a new drug to market than
2 it does a new device. Chris Adams here at the FTC and
3 others have looked at this. It's very costly. I see
4 Joe DiMasi there, the 802 Million Dollar Man, so it's a
5 very expensive, very costly product. It takes many
6 years, quite unlike other healthcare products and
7 services.

8 Secondly, two additional factors are typically
9 required. Not only patent protection, but also FDA
10 approval, so these are, if you will, barriers to entry.
11 They're not insurmountable barriers certainly, but they
12 are barriers to entry, and the long lead times and lag
13 times distinguish them and create some problems which
14 we'll be talking about today, I'm sure.

15 So that's conditions for entry.

16 Let me go to the bottom first now. Once the
17 product is on the market, we have another sort of
18 distinguishing feature of the pharmaceutical industry,
19 and that is cost conditions are really quite perverse in
20 some senses in that once discovered and developed, often
21 there's a very, very low marginal production cost. I've
22 said the first tablet is a mega cost, 800 million or
23 whatever it is, that number. The second tablet for many
24 pharmaceutical products is a dime in terms of marginal
25 cost. This is unique to healthcare, but certainly is

1 not unique to industry in general. In some senses, the
2 pharmaceutical industry resembles the telecomm industry,
3 more generally digitized industries in that scale up and
4 marginal cost can be quite easily accomplished.

5 So this creates all sorts of problems. I might
6 just add here that this is quite different than for some
7 of the biologics which have a substantial production
8 cost at the margin and manufacturing complicity, and Dr.
9 Ryan will probably tell us a little bit about vaccines
10 in that context as well here today.

11 Let me back up here. So conditions for entry
12 are different. Cost conditions are typically different,
13 and finally, conditions for exit are quite different in
14 this industry. Loss of patent protection is often, not
15 always but often reasonably predictable, and typically
16 is followed by very rapid loss of market share. I know
17 of no other industry in which very dramatic reduction in
18 sales and price can -- takes place through no fault of
19 the manufacturer, simply because of patent protection.

20 The other way in which this exit occurs at times
21 is with product withdrawals or recall, and here I think
22 it's interesting to compare this industry with the
23 device industry. This last summer there were a number
24 of recalls and so on of devices, defibrillators,
25 batteries and, things like that, and the manufacturer

1 just carried right on.

2 It's quite different for pharmaceuticals when
3 you have a product like Vioxx or one of these other
4 products withdrawn. It really is quite dissipating to
5 the firm, and what's also sort of interesting is some of
6 the liability issues this raises. I had not realized
7 until this summer that, for example, when battery --
8 defective batteries or other sort of defective product
9 issues result in a recall of a device, an implantable
10 device, that Medicaid pays for the procedure to in fact
11 replace it. It doesn't pay for the new device but it
12 pays for the medical procedure and any of the
13 hospitalizations that result. It's quite different for
14 pharmaceuticals.

15 All right. So, these three conditions I think,
16 conditions for entry, cost condition once on the market,
17 and conditions for exit are quite distinguishing
18 features of this industry.

19 What are some of the economic implications of
20 this? The first thing: Patent protection is extremely
21 important. It's therefore litigated very, very
22 intensively. It raises interesting issues of whether we
23 could have a system that more efficiently handled this
24 litigation with say patent challenges or something like
25 that but it is clear that I think patent protection

1 makes this industry somewhat unique.

2 Given the very low marginal production cost, the
3 industry and the fact that these heavy sunk costs of R&D
4 creates enormous incentives for differential pricing,
5 price wherever you can -- even if you only charge 15
6 cents instead of \$4, it still pays at the margin.

7 Therefore it also increases incentives for
8 advertising that might change the shape or the slope or
9 the level of the demand curve, and finally, and I think
10 this is one of the things that's often overlooked, it
11 creates tremendous incentives for finding new uses for
12 the products.

13 We talk a lot about the small number of new
14 drugs that have been approved by the FDA over the last
15 few years, but if you look at the number of new
16 indications for which the manufacturers have gotten
17 approval, some of these new indications and secondary
18 approvals are much larger -- involve much larger patient
19 populations than the initial approval, that record looks
20 pretty good, and so there's enormous incentives for
21 follow on research in this industry that are somewhat
22 unique to it.

23 Then finally, of course, is this morning's Wall
24 Street Journal reported news on profitability, there's
25 always a perpetual public relations battle here,

1 perception battle on just how profitable is this
2 industry given its strange cost conditions and
3 conditions for entry and exit.

4 So finally, let me just close with some of the
5 issues this raises, some current issues and some that
6 I'll conjecture will become more important. Again, the
7 first four issues here are all related to information,
8 which I think is well very important in healthcare and
9 in the pharmaceutical industry. First is a transparency
10 and disclosure of clinical trial results. We now have
11 the major medical journal saying that they will not
12 publish articles unless all the trials supporting it
13 have been registered at the time of inception, so there
14 are -- and exactly how much trial results will be made
15 public raises some interesting issues, even between, for
16 example, medical journals and public register as to who
17 gets first rights.

18 The global outsourcing of clinical trials is a
19 very big new phenomena. It raises issues about what do
20 we mean by informed consent. It raises issues of are we
21 running trials abroad that are quite different than what
22 we would do here in the states.

23 Regulation of direct to consumer advertising,
24 we'll hear a fair bit about that today, and here one of
25 the issues is it's the content, how much risk versus

1 benefit. Any industrial organization economist will
2 tell you that it's very difficult to regulate content of
3 advertising, extremely difficult.

4 Off label promotion and marketing raises lots of
5 other issues. In the electronics issues, there's a
6 whole literature on how important it is that there's a
7 user induced innovation where the customer gets back to
8 the manufacturer and says, Hey, if you change this and
9 that characteristic, it really will improve things. We
10 call that off label. In medicine it's price pejorative,
11 but quite frequently that can actually result in
12 improved therapies, better dosages and things like that.

13 Importation of prescription drugs into the U.S.
14 remains an issue. It's certainly mooted given Medicare
15 Part D introduction this January, but now as the donor
16 hole becomes more visible, it may reemerge again later
17 this year, particularly after the election.

18 There's a whole set of debates concerning
19 authorized generics. These are brand firms that use
20 their NDA to authorize a generic -- authorize entry by a
21 generic firm; thereby creating competition for let's say
22 one of the generic firms that may have been awarded
23 paragraph 4 exemption, and that raises both issues in
24 the short run and in the long run.

25 I won't comment on that further here, but that

1 may come up later today, and conditions for the entry of
2 bio similars. We have the biotech products now coming
3 of age and starting to lose patent protection. They're
4 quite different. They're not synthesized molecules.
5 They're living organisms. They mutate, and so
6 establishing the criteria on bio similarity raises
7 interesting scientific issues with enormous economic
8 implications, and finally, if we were to meet again in
9 five years, what would I predict might be one of the
10 more interesting new topics? I would think it's this
11 last one. Because of developments in medicine that let
12 us document the role of genetic diversity and how that
13 effects patient's responses to various medicines, we're
14 I think going to be practicing more and more what they
15 call stratified medicine.

16 That is to say, once we've done a diagnosis,
17 we'll have to go a step further to find out what will be
18 the optimal therapy for this particular patient having
19 that diagnosis and that will depend in part on various
20 biomarkers and genetic testing.

21 So what this does is this introduces a
22 combination that the literature is now calling
23 theranostics. What theranostics are is a combination of
24 a diagnostic with a medical therapy, and this raises
25 very interesting issues on bundling, what if the owners

1 of the diagnostic and the therapy are different or the
2 same? That then opens up issues of double
3 marginalization and bundling, and if you think we now
4 have incentives for differentiated pricing, just
5 planning what could happen once we got genetic testing
6 involved. It could really get us closer to first degree
7 price discrimination from our classic textbook
8 treatment, so I think this whole professional move to a
9 more stratified medicine is going to keep the FTC quite
10 busy several years from now it.

11 Thank you.

12 (Applause.)

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1 PRESENTATIONS: INCENTIVES FOR NEW DRUG DEVELOPMENT

2 CHAIR: CHRIS ADAMS, FTC, BE

3 PRESENTER: MARK DUGGAN, Maryland

4 DISCUSSANT: BAPU JENA, RAND

5 PRESENTER: TOMAS PHILIPSON, Chicago Harris

6 DISCUSSANT: DAVE VANNESS

7

8 MR. ADAMS: Thanks, Ernie. For those people who
9 don't know me, I'm Chris Adams. I want to thank
10 everybody who listened to or read all my Emails, even
11 the really long ones.

12 The other person I wanted to thank is Ernie
13 Berndt for helping me organize this conference and for
14 helping me with names and suggestions. That was really
15 great.

16 So what we're going to do now is we're going to
17 go in to the next presentation. I have Mark on first.
18 Do you want to go up first? So we have Mark Duggan from
19 Maryland, and the Brookings Institute. I'll give you a
20 time limit.

21 MR. DUGGAN: 20 minutes?

22 MR. ADAMS: About 20 minutes.

23 MR. DUGGAN: You'll interrupt me as well?

24 (Discussion off the record.)

25 MR. DUGGAN: Thanks very much I guess, F 5 I

1 think I learned. I don't know that from my own, but F
2 5, right.

3 So thanks very much, Chris, to you for
4 organizing this and for inviting me to present. I'm
5 really looking forward to hearing all the talks today.
6 I'm going to start out by talking about some work that
7 I've recently been doing in which I've been trying to
8 estimate the impact of medical innovation, and the paper
9 that I'm presenting today represents joint work with my
10 colleague at Maryland, Bill Evans.

11 So essentially in this paper, we're going to be
12 looking at the affect of HIV antiretroviral treatment
13 and I should say at the outset that we're not looking at
14 all impacts of these drugs. We're going to focus on two
15 particularly, that is healthcare spending, and on
16 mortality, and there are other measures that one could
17 consider, and today though we're going to focus on those
18 two. Those seem like two pretty important ones to us.

19 In doing this, we end up focusing on a
20 particular group, that is individuals who received their
21 health insurance through the federal, state Medicaid
22 program. We're using data from the State of California,
23 and it turns out that although Medicaid insures about
24 1/6th of the U.S. residents, approximately half of
25 people with HIV AIDS in the U.S. are on Medicaid, so at

1 some level, if we were estimating the effect of I don't
2 know plastic surgery, Medicaid would not be a good
3 population to consider, but for HIV AIDS, actually turns
4 out that they are disproportionately represented among
5 the Medicaid population.

6 So just to give you a bit of background before I
7 head into the specifics, as we all know in the U.S. and
8 in other industrialized countries, healthcare accounts
9 for a large and rapidly growing share of GDP. Almost
10 one in every six dollars of GDP now falls into the
11 healthcare sector.

12 This is also true, perhaps even more so, for
13 federal spending. If we look, for example, at Medicare
14 and Medicaid in the 2005 fiscal year, they accounted for
15 about 22 percent of federal spending, but this is
16 projected to rise to 35 percent by 1016 and to continue
17 rising beyond that point.

18 Now, at some point, I guess if you do the trend
19 it can't go above a hundred, I don't think, but in any
20 case, it's clear that it's rising quite rapidly, and I
21 think a key driver of this is really the introduction
22 and subsequently diffusion of new treatment, which tend
23 in general on average to be more expensive than their
24 predecessors, at least in terms of their nominal price.
25 They may have effects on other categories of spending.

1 So today, we're sort of interested in the
2 question of, Are the benefits sufficiently large to
3 justify the cost, and as I said, I want to say that
4 we're not considering all outcomes that one might want
5 to consider. We're going to be focusing today on
6 mortality, but it's certainly not obviously that they
7 would be sufficiently large to justify the cost given
8 the demand side incentives that exist in the healthcare
9 sector generally, and in the Medicaid program
10 specifically, so in general most Medicaid recipients
11 don't share at all in the cost of their medical care,
12 and so that is -- that's something that it's plausible
13 that some treatments have benefits below the price to
14 the Medicaid program given that people aren't facing
15 that price.

16 There's also imperfect information as Ernie
17 noted in his opening remarks about the benefits of new
18 treatments, and so people may not have a perfect sense
19 of what their true increment to health would be from
20 alternative treatments.

21 Because of the in healthcare spending, the
22 projected rise in healthcare spending, it seems
23 plausible that studies that sort of try to think about
24 this, this issue of benefits versus cost, are going to
25 be more important, and it's possible that this is a

1 lever, perhaps a lever to add to other possible levers
2 for reducing the growth rate of healthcare spending.

3 Within the healthcare sector, really the
4 dominant method for evaluate the effect of treatments is
5 the random assignment clinical trial. These are
6 certainly used by the FDA in determining whether or not
7 to approve treatment, but I think it's worth noting,
8 many people here I think would agree, that there are
9 quite a few significant limitations to these randomized
10 clinical trials.

11 In general, they do not consider healthcare
12 expenditures. The FDA certainly does not, and very few
13 randomized clinical trials consider healthcare spending
14 because, as Ernie pointed out, they're very expensive to
15 run, and so these -- and to get sufficiently large
16 sample sizes to get good estimates for expenditures
17 would be very costly.

18 Additionally, trials really are an idealized
19 control, rather than real word setting. There's some
20 question about once a treatment is diffused and it is
21 approved and diffuses into the general population,
22 whether use there will mimic the use in the randomized
23 clinical trials. Also, the studies do I think a good
24 job of estimating average effects, but aren't very good
25 at capturing heterogenicity in those effects. At some

1 level, one may be interested, for example, in the effect
2 for the marginal patient on the margin, if we were to
3 rein in use of this treatment by 10 percent, let's say,
4 what would the effect of that be, and that could be very
5 different from the average effect.

6 Also, these studies tend to have short time
7 periods and small samples sizes, and so an alternative
8 way to -- but they do have the benefit of randomization
9 which is huge. If we look out in the real world at a
10 cross-section of patients, some who get a treatment and
11 some who don't, there's likely to be many differences
12 between them that we can't capture perhaps from
13 observational data.

14 However, I think there are -- there is some
15 scope for studies with observational data to complement
16 these randomized clinical trials, especially in the
17 period right after a new treatment has been approved and
18 starts to diffuse into the population.

19 In a sense, that creates a possible source of
20 exogenesis in treatment use, in that in period T, of
21 treatments unavailable, and in period T plus one, it is
22 available.

23 So as I said a minute or two ago, in this study,
24 we're focusing on the effect of HIV antiretrovirals, and
25 I should note at the outset that these are by no means

1 representative of your sort of healthcare treatment,
2 innovations over the past couple of decades. Clearly
3 there have been huge reductions in mortality for this
4 population, and so one might think that this is one of
5 the greatest -- arguably the greatest success story of
6 healthcare innovation in the last couple of decades.

7 The randomized clinical trials suggested large
8 benefits from some of the treatments that were released
9 in late '95 and early '96, and these treatments received
10 expedited FDA approval as a result. The four that I'm
11 thinking of and that I'll talk about in a bit are Epivir
12 and protease inhibitors, and it's clearly that after
13 these treatments were introduced, mortality from HIV
14 AIDS fell, and this was especially true from 1995 to
15 1997, and so we're going to use this as a way to sort of
16 to think about estimating the impact of innovations with
17 observational data, and in the back of your mind, you
18 want to have the kinds of concerns that are healthy to
19 have about any study that uses observational data.

20 For example it turns out that sicker patients
21 are going to be the ones who are more likely to take
22 these drugs, so if we did a naive comparison of those
23 taking the drugs and those not taking, we might observe
24 the same mortality rate between the two groups when in
25 fact the drugs are having huge or are reducing mortality

1 to a huge extent.

2 So that is the kind of thing to have in the back
3 of your mind.

4 So here we can all kind of agree, if you look at
5 this figure, this represents the number of deaths among
6 U.S. residents with AIDS over a 24 year period, and we
7 can see that this was steadily rising through '94,
8 flattened out in '95, and declined steadily during the
9 next two or three years, and you would be hard pressed I
10 think to find a graph like this for many things in the
11 last two decades. I'm sure there are some things, but
12 it's a pretty impressive and important in the well-being
13 of individuals with this illness.

14 So one can sort of look at well by the end of
15 1993, there were about two dozen drugs approved for the
16 treatment of HIV AIDS. Let's think about possible
17 candidates for -- that could have contributed to this
18 massive fall that we saw.

19 You see that basically Epivir, released in late
20 1995, and the first three protease inhibitors released
21 in this late '95, early '96, their release dates
22 coincide pretty well with that remarkable break in trend
23 that we observed in this figure.

24 So it's not just from this. I think other
25 studies have suggested that the protease inhibitors and

1 Epivir did contribute to big reductions in mortality, so
2 in terms of trying to estimate the effect of these
3 antiretrovirals, I'm going to propose a fairly simple
4 model in which we're trying to estimate the effect of
5 some treatment, Z, on some outcome, Y, for individual J.

6 And the parameter in which I'm interested in
7 here is this parameter beta, which represents the effect
8 of that treatment on the outcome variable Y, and this
9 effect could vary both across patients at a point in
10 time. Some people may deliver -- may obtain a bigger
11 benefit from treatments, and also even within a patient
12 over time. Perhaps as a patient's health deteriorates,
13 they would get a bigger benefit, and that kind of
14 heterogeneity, is an important thing to have in mind.

15 Another important thing here is to think about
16 this baseline health status which we model as H. In a
17 sense it turns out that the guidelines for the treatment
18 of the use of ARV suggests that patients not initiate
19 treatment until their health deteriorates to a certain
20 level, so in general we're going to have sicker patients
21 tending to take the treatment, and this is going to
22 serve, to some extent, to bias against finding that
23 these treatments reduce mortality for the reasons that I
24 mentioned at the outset.

25 So it's really crucial to control for baseline

1 health status H. That's kind of one source of
2 endogenics that we want to have been in mind. At that
3 beta, it's plausible that the people who are likely to
4 derive the greatest benefit for the treatment, the ones
5 with the largest value of beta, are going to be the ones
6 most likely to take it, so to some extent, if we wanted
7 to know beta for everyone looking just at the treated
8 population would perhaps give an inaccurate estimate.

9 So there's kind of two sources of heterogeneity
10 there that are important, underlying health and
11 treatment effects.

12 For this we're going to be using data from the
13 California Medicaid program that has claims and
14 enrollment data for 24 percent sample of California's
15 Medicaid recipients over an 11 year period.

16 This data has been linked to mortality data for
17 the State through the end of 2001, and the encrypted
18 Social Security numbers in this data allow us to link
19 individuals over time so that we can follow people for
20 up to 11 years, from early '93 all the way through the
21 end of 2003 if they live that long and remain on the
22 Medicaid program that long.

23 There's really detailed information on
24 healthcare utilization in our sample, both before and
25 after the release of the new treatment, so that's kind

1 of important for us. We're going to be able to control
2 for differences across people and their health status at
3 the instant that these treatments were released.

4 Imperfectly for sure. We don't have the same
5 kind of detailed clinical data that physicians would
6 have, but I think it's -- it's important to be able to
7 control in a reasonably good way for this baseline
8 health status, and our sample of individuals includes
9 more than four million individuals with one or more
10 months of eligibility during this 11 year period, and if
11 you do a little head math, dividing 4 million by .24,
12 you will see that about 16 and a half million
13 Californians were on the Medicaid program during this 11
14 year period, almost half of the state touched this
15 program during this 11 year period. It's a pretty big
16 number.

17 Now, though, once we start to focus on people
18 with HIV AIDS, our sample size falls by about 99.7
19 percent, so it's good that we're not doing this study in
20 Wyoming. Nothing against Wyoming but we would have
21 about 7 people left I would think.

22 So we're going to select the 13,000 individuals
23 in our sample with two or more claims with a primary or
24 secondary diagnosis of HIV and who have consistent
25 demographic data across years. We're going to drop

1 about 2,900 people who are in managed care and for whom
2 we'll have incomplete information, and we talk in the
3 paper a bit about should you be worried about that or
4 not. We think we should be, but we try to minimize the
5 problems with that but it's something to have in mind.

6 We have a final sample of a bit more than 10,000
7 patients, and individuals are going to enter our sample
8 in the quarter of their first HIV claim, and so it's
9 worth having in mind that we don't know -- there are
10 lots of issues here. It could be that people have had
11 HIV aids for a long time, and then become eligible for
12 Medicaid after they've lost their job and spent down
13 their assets, and so we don't necessarily have a
14 complete medical history on people but we still do I
15 think have a lot of baseline health information.

16 So I'm going to start off with a graph, which I
17 think provides some pretty transparent evidence for,
18 number 1, treatment patterns changed enormously
19 following the introduction of these new treatments in
20 1995, and second, health outcomes, at least measured by
21 mortality, fell in a similarly striking way, and so if
22 you look here in our data, basically the fraction of our
23 sample, taking one or more HIV drugs in each quarter, it
24 was pretty stable at about 30 percent through the last
25 quarter of 1995, and then during the subsequent year and

1 a half, it approximately doubled, going from 30 to 60
2 percent, so in thinking about the effect of these
3 treatments, you kind of want to have in mind two groups.
4 First, the group who was taking ARVs at the time of the
5 approval of these new ones, call that group A, and this
6 group B that was -- wasn't taking a treatment at that
7 time and started to take on -- and so the sort of
8 aggregate effect of this treatment is going to be some
9 combination of the effect on both of these groups, at
10 least on the outcomes that I've described, mortality and
11 healthcare spending.

12 And so if one looks, pretty much all of this
13 increase was driven by an increase in the use of Epivir
14 and protease inhibitors. If we look during this period,
15 zero percent were using this treatment in the third
16 quarter of 1995, and 57 percent were using it by the
17 first quarter of 1997, a pretty big change in treatment,
18 and right along with that you see a pretty massive
19 decline in mortality, from about 7 percent per quarter,
20 which is almost a 30 percent annual mortality rate, to
21 about 2 percent per quarter, and that's about 70 percent
22 decline in mortality.

23 So that sort of suggests that there has been
24 this big effect on mortality. What about for Medicaid
25 spending? It's definitely true that the new ARVs are

1 more expensive than their predecessor. On top of that
2 people are often taking multiple treatments whereas
3 before they might have been taking only one, and so it's
4 not surprising that spending on these drugs increased by
5 more than a factor of 8 during a two-year period.

6 However, it is also plausible that this offsets
7 spending on other quart -- other categories of medical
8 care. For example, hospital case, et cetera, and so
9 it's interesting to look at, here you can see that
10 pretty clearly in a graph. Spending on other categories
11 of medically care here labeled inpatient and outpatient
12 was pretty flat through the end of 1995, and then once
13 these treatments were released, it went down by a pretty
14 large amount, especially from '95 to '97.

15 It's interesting to note though, after '97,
16 there isn't much further decline in this patient and
17 outpatient spending despite the fact that prescription
18 drug spending continues to rise.

19 So we can look at this as even more simply
20 trends in the distribution of Medicaid spending, and I
21 think here this table can help us to think about the
22 herterogenous effects of these treatments on
23 expenditures, so if you look, for example, for the
24 median patient, spending seems to have gone up slightly,
25 because for that person, there wasn't much medical care

1 to offset. They weren't going to the hospital at
2 baseline, and so if anything, here you see -- spending
3 for them, if you look in the 50th percent column,
4 spending there going from about \$1,700 to \$2,700 over a
5 two-year period.

6 However, spending at the high ward -- at the
7 high ends of expenditure distribution really did fall a
8 lot because these are people for whom, if you can reduce
9 hospital care you're really going to potentially save
10 some money, and those two to some extent approximately
11 offset. On that we think that the spending for people
12 not actually eligible for Medicare, which given 20
13 minute, I don't have a lot of time to go into the
14 details of that, looks like spending fell by about \$700
15 per quarter per person.

16 Okay. So given I have about 3 minutes left, I'm
17 going to go through very quickly -- I guess I'm just not
18 going to have much time to talk about my individual
19 level analyses. Suffice it to say, the take away from
20 table 4 is that the effect of these treatments on
21 mortality went quite a lot across patients.

22 People who were in very bad health at the time
23 these patient -- these treatments were released saw
24 really large declines in mortality, whereas their
25 counterparts, who were -- had had a few claims and were

1 probably not in such bad health that the disease hadn't
2 progressed so far for them, there was not such a big
3 absolute percentage point decline in their mortality
4 rates.

5 Similarly for spending, once again, little
6 effect on spending for those who were relatively
7 healthy, brief declines, and you can see the
8 heterogeneous effects on mortality here from this graph
9 in which we sort people into five different quintiles,
10 the sickest people are in the top quintile: Their
11 quarterly mortality rates were about 17 percent at
12 baseline. The healthiest people in the lowest one,
13 their baseline mortality rate is about 2 percent, and
14 you see massive reductions in the highest quintile.
15 This sort of captures the effect of these treatments.

16 So to summarize the individual level results,
17 the effect of the new treatments on mortality varies
18 across patients, and our estimates are quite close to
19 what was obtained from the randomized clinical trials
20 regarding effect of these things on mortality, so that's
21 a good thing, suggesting that in the real world, people
22 were doing a very good job complying with this
23 recommended treatment regimen, and the short-term
24 expenditure effects also vary with health status.

25 In terms of long-term spending, there are kind

1 of two things essentially going on. First, in the
2 short-term our finding suggests that spending per
3 quarter fell slightly by about \$7,700 or 10 percent per
4 person, but the fact that people are living so much
5 longer means that the long-term spending on the Medicaid
6 program is going to go up by more, and you can see
7 this -- I guess I don't have this graph, I took this out
8 trying to get the slides down, but basically if you look
9 at spending rather than over a one year period, over a
10 six year period, it's very clear that that has been
11 going up quite rapidly.

12 However, if you just try to calculate, just a
13 very simple calculation, increase in life expectancy
14 versus increase in projected spending, it's clear that
15 these treatments pass a cost benefit test, in that they
16 basically cost the government, through the Medicaid
17 program, about 22,000 per life year saved trying to hold
18 everything else fixed in the healthcare system, so we're
19 trying to disentangle the effect of Epivir and protease
20 inhibitors holding constant everything else in the
21 healthcare system, which is kind of a difficult thought
22 experiment, given that other things are changing so
23 rapidly.

24 And so just to wrap up on this -- here we're not
25 including Medicare spending which may make 22,000,

1 30,000, but still as I said, well within the range of
2 cost effectiveness. Okay, one minute, good I'm on the
3 discussion slide. So here we're using longitudinal
4 claims data for individuals from before and after the
5 introduction of new treatments, and in our view this
6 provides a plausible exogenous source of variation with
7 which to evaluate the effect of innovation, and the
8 utilization varies over time and across groups, and we
9 think that this kind of approach, whenever a new
10 treatment hits the market, could be employed to try to
11 evaluate the effect of medical innovations in the real
12 world, using lots of baseline information, looking at
13 how things appear, right prior to the release of these
14 treatments and then following things immediately after,
15 because in the real world it can differ from those in
16 the trials, and on top of that, we can't learn anything
17 really about spending from the trials.

18 The effects here vary substantially across
19 patients. There's definitely not flat of the curve
20 medicine for these treatments. Maybe there are for
21 others. There are more than 12 treatments approved
22 since these four, and we haven't seen a much further
23 decline in mortality but maybe that's masking
24 improvements because the characteristics of these folks
25 is changing over time.

1 But it's kind of surprising to me that similar
2 studies like this are not done more often, are not
3 encouraged more given that Medicaid let's say in 2004
4 spend 39 billion on prescription drugs.

5 In fiscal year '06, my hunch is Medicare and
6 Medicaid spending will be about \$700 billion, about
7 \$6,000 per household in the U.S., and so you might think
8 that we might want to think a little harder about
9 evaluating what we get for that, and 650 in 2005, 700
10 billion in 2006 for all that spending.

11 One last table, here you can see that
12 pharmaceutical treatments, as a share of all Medicaid
13 spending, these are rising quite rapidly from 1995. We
14 saw that about 7 percent of Medicaid spending was on
15 prescription drugs, and in 2004, nine years later, that
16 had almost doubled.

17 So prescription drugs are becoming a more and
18 more important part, at least measured by spending, of
19 the healthcare delivering in the Medicaid program, which
20 currently provides insurance to about 50 plus million in
21 the sum.

22 So thanks for not interrupting me.

23 MR. ADAMS: Let's give him a round of applause.

24 (Applause.)

25 MR. ADAMS: Now we're going to have Bapu Jena,

1 who is a Ph.D. student at Chicago, and currently is at
2 RAND enjoying the California weather.

3 MR. JENA: Yes, at bit. I think the last time I
4 used this was at a wedding, but let's see how do we get
5 down here.

6 So let me start by saying I like paper a lot,
7 and I like a lot of Mark's work in general, so the
8 balance of my comments will mainly be suggestions as
9 opposed to critiques.

10 So other than demonstrate that these HIV drugs
11 have been tremendously beneficial in terms of reduced
12 mortality, I think the main conclusion that I took from
13 this paper was in a well specified econometric model, we
14 can get good estimates of reductions in cost, in changes
15 in costs and the effectiveness of medical treatment.

16 The main advantage I think from this paper is
17 there's three things: One is you get big sample sizes,
18 and you get longitudinal data so you can look at
19 mortality, and I think Mark alluded to this in his
20 paper, rare side effects, which is a big deal for HIV
21 drugs.

22 Secondly, randomized trials often look at
23 placebos as controls, depending on what the standard of
24 care is, and I think finally the biggest point to take
25 is that you can use these types of data sets to look at

1 how drugs are used in the real world and how effective
2 they are in real world settings.

3 Finally I think this is a good response to the
4 new Institute of Medicine report arguing for more
5 systematic approach to post approval studies, so just a
6 few questions. Mark highlighted the potential downward
7 bias in estimates because you don't control for clinical
8 need. One question is for these type of drugs, we know
9 their side effects are a big issue, so within a clinical
10 categorization somewhat with a certain CD 4 count is the
11 potential for an upward bias if you don't take into
12 account side effects, and people that don't take the
13 drugs because of side effects are going to be the ones
14 who are least likely to benefit, so you could get a
15 potential upward bias.

16 To Mark's benefit though, I think he finds that
17 the randomized control trial data is pretty similar to
18 what he finds in this real world setting, so it could
19 argue that the observed attrition that's thought to be a
20 problem in clinical trials is actually not so much of a
21 problem because it's kind of mimicked in real world
22 settings.

23 A second question is Mark focuses on the
24 mortality effects of drugs, so as we all know, AIDS is a
25 disease characterized by a progression from overall

1 healthiness to an often prolonged period of illness and
2 ultimately death, so one thing that you could look at
3 potentially in this data is what is the effect on health
4 outcomes.

5 We know that these drugs also slow the
6 transition from HIV AIDS as opposed to AIDS to death, so
7 one way we could do this is to look at people who have
8 HIV only as opposed to full-blown AIDS and look at
9 whether or not pre and post the introduction of Epivir
10 and these protease inhibitors do we see changes in
11 claim, the types of claims and the number of claims for
12 these types of individuals.

13 The final question relating to the next talk is
14 these drugs are obviously very cost effective. What do
15 I mean by cost effective? Will the benefits consumers
16 far outweigh the costs? What are the implications of
17 those findings, for incentives, for innovation for firms
18 when the benefits far outweigh the costs? Do they have
19 enough incentives? If it's not the case, one thing that
20 we might think of is an absence of market power.

21 As Mark demonstrated, with these drugs, that's
22 probably not the case. The demand this faces is very
23 inelastic, and prices are high, suggesting a low, low
24 elasticity to demand, and ability to discriminate a
25 little bit better. That's it.

1 MR. ADAMS: Mark, did you want to respond to
2 anything, or do you want to come up and maybe answer
3 some questions?

4 If we have questions, can you just raise your
5 hand and we'll have somebody come over to you?

6 MR. DUGGAN: I'm going to just respond for a
7 second to Bapu's comments, so yeah, thanks for those
8 comments, and so I think looking at other measures of
9 health outcomes definitely is a natural next step for
10 the paper and, for example, the side effects and the
11 transition rates from HIV to AIDS, and we haven't
12 thought much here at all, and I'm going to leave this to
13 the next paper, about sort of innovation incentives and
14 that kind of thing, whether -- given what we're finding,
15 is there too much, too little innovation for this
16 category of drugs, but I think that's a hugely important
17 issue that we just punt, but, that's a good thing to
18 raise, so I'm happy to answer if anyone has questions.

19 MR. AZOULAY: Pierre Azoulay from MIT. So I'm
20 very interested in the paper. There's a huge literature
21 in bio stats about estimating the effects of ARVs from
22 observational data. Now, this literature is not all
23 concerned with heterogenous treatment effects. They're
24 sort of replicating trying to see if we can sort of
25 replicate the effect of randomized trials from the

1 observational data, but one thing they seem to sort of
2 conclude quite strongly is that it's sort of wrong to
3 control directly for potentially some time varying
4 status, basically the CD 4 cell count in the type of
5 data they usually have, sort of on the right-hand side
6 of the regression because in a sense the estimate that
7 you get then is consistent but doesn't have sort of a
8 clear causal interpretation because selection to
9 treatment depends on in a sense these baseline status,
10 so you have sort of a feedback effect.

11 MR. DUGGAN: That's kind of a direct versus an
12 indirect effect. That basically if you take the
13 treatment, let's say your CD 4 count is 1,200 or 150,
14 and as a result your CD 4 count goes up, right, you're
15 not going to capture that if you control for the CD 4
16 count, there's going to be this effect on the CD 4 and
17 you're not capturing that in your estimate for the
18 effect of the AVR. I think there's some literature,
19 this literature sounds irrelevant, but something about
20 fertilizer, like there's a literature -- there's a
21 problem about the direct and indirect effect, yeah, is a
22 big issue.

23 We here try to just look at what the health
24 status is at the time these things are released.

25 MR. AZOULAY: They seem to be time varying.

1 MR. DUGGAN: We did two different sets of
2 analyses, so we did one set in which -- the problem if
3 you don't -- if you allow it -- am I talking too much?
4 I usually do talk too much, but the problem, if we don't
5 allow it to time vary, the problem is that you see --
6 you lose many more people who are sick, right, and so
7 you have these weird compositional changes. You don't
8 lose anyone from the lowest quintile.

9 You're losing lots of people from the highest
10 quintile, and so how -- so I don't think either way --
11 so we do both, and they both point to the same
12 estimates. When you don't allow it to vary, the health
13 status to vary, we get slightly higher estimates for the
14 effect, which is consistent with what you're describing,
15 that this indirect effect we're understating the effect
16 of the treatments on mortality, right, so that's an
17 excellent point and something that we try to make in the
18 paper but maybe don't do well enough.

19 MR. ADAMS: Let me cut you off and let the next
20 speaker talk and it's a very complimentary paper. We
21 have Tomas Philipson from Chicago, who's going to talk
22 about the question that Bapu raised, and he raised it
23 because he's the coauthor on the paper.

24 MR. PHILIPSON: Okay. I'm going to report on
25 some work that is joint with Bapu Jena who was just up

1 here discussing -- Bapu has just completed his Ph.D. in
2 economics and also pursuing an M.D. at the same time,
3 which can keep you kind of busy, and I am going to talk
4 about basically it's a very complicated title for a much
5 simpler topic but essentially the R&D incentives
6 involved with formal technology adoption procedures,
7 which are typically used in Europe, and I will argue
8 having spent time in CMS are sort of implicit used in
9 the U.S. as well, even though not so explicit.

10 So the motivation for considering this is
11 essential, which is a common claim by health economists
12 that new technology is the driving force behind growth
13 in healthcare spending. That's not so much because we
14 have documents as well as Mark and others just did.
15 It's more of like most economic growth due to
16 technology -- technological change in economics is sort
17 of what we can explain with other things.

18 So it is also seems sort of self-evident that
19 there are a lot more technologies out there than there
20 was 30 or 40 years ago that we are spending money on,
21 and so it's not just resorting to an unexplained growth,
22 but it seems very plausible, so there's a belief that
23 since Newhouse I believe was the main impetus of this
24 belief in '92 or '93 is technological change is the
25 reason healthcare spending is growing faster than the

1 rest of the economy.

2 So that naturally raises the question, if that's
3 the case, how do we manage these new technologies. We
4 have a lot of literature on managed care. We don't have
5 so much of the literature on managed innovation, if you
6 want, how do you basically manage this inflow of new
7 technology that comes on the market, and we understand a
8 lot more about the ex post problem of once you have a
9 technology, how do you use it than we understand I
10 believe the ex anti problem, how do you manage the sort
11 of entry of these new technologies into the market.

12 Now, there is a literature, and in fact the
13 biggest literature in the whole area or field of health
14 economics concerns what's called cost effectiveness
15 analyses, which is an enormous literature in Europe, and
16 I'm pretty sure it's probably the biggest field within
17 health economics if you view health economics in a world
18 sense, maybe not so much in the U.S. health economics
19 field.

20 But it hasn't I believe been connected very well
21 to economic efficiency, how does it relate? Cost
22 effectiveness analysis is essentially -- I'll talk about
23 it, sort of a strange allocative measure of
24 desirability, and I'm going to or Bapu and I are going
25 to in this paper talk about how it relates to economic

1 efficiency, both in a static sense given that we have
2 the technology on the market, and in the dynamic sense
3 of actually reducing the right amount of technological
4 change.

5 So the bottom lines of the paper which I'll
6 iterate later is that essentially of cost effectiveness
7 analysis driving technology adoption which is sort of
8 more explicitly done in Europe, particularly in England,
9 in the sense of letting on the market certain
10 technologies just pass the cost effectiveness test, if
11 you want.

12 It has a lot to do with static efficiency, but
13 it's not so well connected to dynamic efficiency. It
14 basically allows optimal use of a technology that exists
15 but it doesn't induce derived incentives for actually
16 developing that technology.

17 Then we'll go into looking at some ways of
18 essentially inferring whether the right dynamic
19 incentive are in place. We're also going to talk about
20 these HIV therapies that Mark talked about. We're going
21 to have a little bit more aggregate analysis to see sort
22 of what those dynamic R&D incentives look like, and in
23 that context discuss what CA or cost effectiveness
24 analysis would do to innovation incentives, given how we
25 argue how little the innovators of these products

1 capture of the total benefit or social surplus of them.

2 So the first thing we want to do, we were told
3 there was a mixed audience here, some economists some
4 are not. This is a pretty familiar graph to economists.
5 It's a supply and demand schedule, and you basically
6 have what's called consumer surplus and producer
7 surplus, and think of your sort of -- my favorite
8 innovation recently would be the IPOD, so consumer
9 surplus essentially for non economists captures how much
10 you're willing to pay above the price so you might value
11 an IPOD at a grand or something. It's selling at \$200.
12 You have a consumer surplus of 800 bucks.

13 Producer surplus is how much the price is above
14 cost. It might cost a hundred bucks to produce it. You
15 have a producer surplus of a hundred dollars per IPOD.

16 Now, depending upon the price obviously, you get
17 a division of the total surplus, which is the surplus
18 plus to produce the surplus into the consumer camp or
19 the producer camp.

20 Now, that's going to be important obviously
21 later on for cost effectiveness analysis, which we're
22 going to argue is essentially consumer surplus based
23 measure, if you want to interpret it that way. So cost
24 effectiveness analysis is essentially quality adjusted
25 price measure. It's a cost per or price per health

1 unit, if you want, and it's very related to -- in this
2 paper we kind of translate it, for an economist it's
3 very much synonymous with being interested in maximizing
4 consumer surplus. It's essentially the bang for the
5 buck in health that you get for buying a particular
6 product.

7 Now, obviously in the static setting, that makes
8 a lot of sense. We think prices above cost are bad in a
9 static setting, and the larger bang for the buck, the
10 lowest price you get for the same health benefit, the
11 better off are we in social welfare.

12 Markups are bad in some sense, if some consumers
13 can't afford the product even though they're willing to
14 pay the production costs.

15 So it's a measure of consumer or it aims to
16 maximize consumer surplus when you try to have low cost
17 effectiveness, and -- but it obviously does not square
18 off well with dynamic incentives, which are contingent
19 on producer surplus being obtained in the future, so if
20 the 802 million dollar man is sitting in the audience,
21 if you're investing that amount of money, you're
22 presumably doing that hoping to get back a little bit
23 more than \$802 million in the future.

24 So it's contingent on essentially future profit
25 producer surplus, and merits mean having very high cost

1 effectiveness or high consumer surplus in the future
2 becomes a problem because it also has -- means low
3 producer or low producer surplus and therefore lower
4 incentives for innovation.

5 Now, the most extreme clash with cost
6 effectiveness and efficiency you can think of when you
7 have a very -- a good price discrimination in the market
8 for the product, so if you have perfect price
9 discrimination, you can think of the producers pretty
10 much capturing the entire social surplus, being able to
11 charge consumers exactly the thousand dollars they were
12 willing to pay for the IPOD, nothing goes to the
13 consumer, everything goes to the producer in terms of
14 surplus.

15 In that setting, you would have cost
16 effectiveness minimized. It would be the lowest bang
17 for the buck for the consumer. They pay just what
18 they're willing -- what they value the product at. You
19 would have -- on the other hand, you would have the
20 dynamic incentives to correct because the producer, when
21 investing is \$802 million on R&D is looking at the
22 social surplus as the return on that investment, which
23 is not so different, by the way, the patient -- the
24 pharmaceutical companies are not so different than
25 people usually believe because a lot of the owners of

1 those companies are patients in terms of their pension
2 funds.

3 So it's not that different gap between patients
4 and pharmaceutical owners as I think is sort of the
5 media portrays. But you have a clash there between cost
6 effectiveness, which would be minimized in that case,
7 and dynamic efficiency, which would be maximized.

8 In addition, health would be maximized because
9 everyone would be getting the product in the sense that
10 everyone would be paying just what they're willing to
11 pay, get the product. Presumably the product has a
12 positive treatment effect on health, and that will lead
13 to the optimal or the maximum amount of health in the
14 population but the lowest amount of cost effectiveness
15 but also the highest amount of dynamic efficiency.

16 So that's sort of a clash between what I think
17 cost effectiveness does, which aims to maximize consumer
18 surplus, with how you think of optimal innovation, where
19 there's sort of a wedge between what motivates an
20 innovator, and actually social benefit of the innovation
21 ex post.

22 And I think that's essentially the gist of why
23 we come down a little hard on how you should interpret,
24 I think, cost effectiveness regulation, particularly one
25 of the English style where you essentially have a ratio

1 that you have to pass in order to get a purchase by the
2 single buyer, and that's essentially a price control in
3 disguise. The effectiveness of the treatment is set by
4 the innovation, what's the effect of the survival of new
5 HIV treatments, for example, that's not regulated, but
6 if you regulate cost effectiveness, you're essentially
7 just regulating price, and the price control is sort of
8 in disguise under the name of cost effectiveness
9 analysis, I think, in those circumstance, and obviously
10 we don't -- innovation and price controls sort of do not
11 go very well. That's why we have patents. We want high
12 prices to motivate innovators, and having price controls
13 on patents is sort of defeating the purpose of patents.

14

15 Now, there are alternative reasons why you might
16 not want to have full appropriation, that is to say, the
17 producer capturing the entire social surplus in the case
18 of biopharmaceutical R&D. One has to do with patent
19 racing where you might get an excessive -- we go through
20 these reasons in the paper, patent races where you get
21 excessive spending for the same idea or where you have
22 publicly subsidized R&D. In the U.S. about half of R&D
23 is subsidized or is public through the NIH, and that
24 might lead to less than full appropriation being optimal
25 for private R&D investors.

1 You have the effects of insurance and moral
2 hazard on optimal appropriation, and also which is sort
3 of unique to this industry, you have what's called -- we
4 call consumer based R&D. That is to say, a big part of
5 the R&D process or R&D spending is on clinical trials,
6 which is essentially early consumers relative to later
7 consumers when it gets marketed, and in some sense the
8 trials are sort of solving an externality problem in the
9 sense that early consumers are having huge positive
10 externalities in their consumption because we actually
11 learn how this stuff is working and could therefore or
12 should or should not -- they're not allowed to by law,
13 but should or should not be there for compensation by
14 future consumers in terms of generating that information
15 from their consumption, and that actually effects
16 optimal appropriation as well.

17 We go through -- to look at -- in this context
18 we wanted to see, Is this a big deal or not, or how well
19 are the appropriations taking place of new technologies.
20 If it's very very high, you would think that cost
21 effectiveness analysis may be an issue. You might want
22 to lower it, depending on these reasons I gave before,
23 or if it's very very low, then you think -- then you
24 possibly would think that cost effectiveness analysis or
25 price controls would be more dangerous in terms of

1 further diluting R&D incentives, so we looked at this
2 for the new therapies, the protease inhibitors that come
3 in in the mid '90s that Mark talked about in a little
4 different way in terms of getting the aggregate values
5 of innovation.

6 So we looked at essentially the gross consumer
7 surplus starting from the start of the epidemic which we
8 took in 1980, discounted back G here from a level
9 measured GT , so we basically look at what's the value
10 of -- for the cohort of people that get HIV in 1989 in a
11 given year T , the number of those people, call them T ,
12 and the value to them of the new therapies that came in
13 in mid '90s is GT , and that may be different obviously
14 depending on when you got the disease.

15 If you got the disease in 1999 after the
16 technologies, you probably benefit a lot more than if
17 you got it in '84 and had to live 11 years and probably
18 died before that to see the new technologies come on
19 market.

20 So how did you value the change in the
21 technological change? We'll use some formulas that we
22 used in another paper to basically look at the different
23 survival curves that Mark talked about, S of T being of
24 a given cohort and an S of zero being some kind of
25 factual survivor off curve you have to construct that

1 would be present in absence of the technological change.

2 And you can do that in very many different ways,
3 and you probably will remain at the same answer, which
4 would mean the overall conclusion we will get later
5 which is that these gains were very, very large, so if
6 you look at the HIV incidence overall in the U.S., you
7 should focus on this kind of bell -- there's a lot of
8 stuff in there but there's sort of a bell shaped curve
9 of HIV incidence which kind of peaked in the mid '80s,
10 and then kind of went down drastically.

11 It's a little hard to estimate on the aggregate
12 level because HIV is basically induced from AIDS numbers
13 that is mandatorily reported, AIDS cases that are
14 mandatorily reported, and then they convolute those to
15 get back at HIV cases that would have had to have
16 occurred to get those AIDS series reported mandatorily.

17 The survival curves that also Mark talked about
18 sort of shift out dramatically. There's a spike cohort.
19 This is since the start of the epidemic since 2000. You
20 sort of get a dramatic shift in this S of T that we
21 talked about, and the question is, How much do you value
22 these, so if you look at a given year of infection on
23 the row, you will see the number of people that are
24 estimated to get the -- get HIV. You will see in the
25 third column individual value would be the -- what is

1 the value of the life years gained for those individuals
2 on an individual level.

3 And then if you aggregate up, you multiply the
4 incidents with individual values, you get the aggregate,
5 and the bottom line of this is that those are very big
6 numbers, so in the trillions or in the trillion I should
7 say, and the way you could think of that is if you have
8 a value life year of say 200 thousand dollars and you
9 gain five years, you have a million dollars for a given
10 individual and you have a million people having this
11 disease over time or having HIV over time, you get up to
12 a trillion very quickly.

13 So that's essentially the source of the large
14 numbers is that the value of a life year is estimated at
15 conventional levels times the dramatic effects on
16 mortality or traumatic effect on increased longevity,
17 aggregating that up over people you get very large
18 numbers.

19 Now, you get very large numbers -- you get very
20 small numbers of that value captured through sales, and
21 in order to economize on time here, I'm going to go to
22 the main implication of this, which would be that about
23 5 percent of the aggregate value, that is the patient
24 value I just talked about, goes to the innovator in
25 terms of profits from selling these products, so you

1 don't have much more than about \$74 billion spending on
2 these products and present value terms since the start
3 of the epidemic, and that's tiny relative to the life
4 years saved times the value of live attached to those
5 life years.

6 So very small appropriation. Then we go on
7 again in the interest of time, to basically look at all
8 the technologies, how can you basically look at how much
9 innovators on program rate of this social return as it
10 relates to cost effectiveness, and then we get sort of a
11 derivation of how much the producer surplus PS is as
12 fraction of the total benefit of social surplus, SS in
13 relation to the cost effectiveness measure or cost
14 effectiveness measure, CE, and they're presumably
15 inversely related.

16 Because of that, we can infer essentially
17 appropriation from cost effectiveness studies, and we go
18 to the Harvard registry of cost effectiveness studies,
19 which is a sort of registry of cost effectiveness
20 measure on a bunch of technologies, and match out
21 essentially what that implies for what the innovator
22 would capture of the technology given the observed level
23 of cost effectiveness. We can convert that into what
24 share of the total benefit to society did the innovator
25 capture, and this is sort of the distribution of that --

1 of those technologies across appropriation shares, and
2 what you will see here is there's about -- half the
3 sample has for the potential or actual, which is not
4 important here, but you can think of between 10 and 20
5 percent of social surplus of these innovations in the
6 Harvard Registry are captured by the innovator, which
7 means roughly that if you're looking at people investing
8 millions of dollars into R&D, they're only seeing about
9 10 or 20 percent of the social value of that new product
10 as the return on their investment, so it's sort of
11 unmotivating them in that sense.

12 How many minutes do I have?

13 So the conclusion very quickly would be
14 essentially that what we looked at in terms of trying to
15 translate cost effectiveness analysis or using cost
16 effectiveness as adoption criteria, particularly in the
17 public sector, which was done more in Europe than here,
18 we basically argued that that has severe social dynamic
19 inefficiencies. It does promote static efficiency, that
20 is to say we should have the technology bringing pricing
21 down to cost seems like a great idea, but that's also
22 why we have patents to avoid that in some sense.

23 So it's basically static efficiency measured by
24 aiming to maximize consumer surplus, and has some severe
25 dynamic efficiencies, and also might actually lower

1 health if under price discrimination more producer
2 surplus means wider adoption or a higher output, which
3 it does under most circumstances.

4 We looked at some examples of how to basically
5 look at what the R&D incentives are as a function of
6 cost effectiveness analysis into what fraction of social
7 surplus is captured by innovators and saw that that was
8 pretty low, and therefore we're kind of led to at least
9 in some current work we're doing to look at what are the
10 exact innovations induced by further suppressing
11 innovative returns by what implicitly are essentially
12 price controls.

13 Thank you very much.

14 (Applause.)

15 MR. ADAMS: We're going to have David Vanness
16 from the University of Wisconsin medical school who is
17 going to give a discussion of this paper.

18 MR. VANNES: Thanks, Chris, if we can find it.
19 There we go. Thank you. I just wanted to start off by
20 thanking Chris from the Bureau of Economics for inviting
21 me today, and it's a pleasure to be addressing you all,
22 and I also wanted to thank the authors, Tom Philipson
23 and Bapu Jena for writing what I thought was a very
24 thought provoking paper, well written. I enjoyed
25 thinking about the issues that they brought up.

1 In particular I thought it really illustrates
2 disconnect between what is done in applied cost
3 effectiveness analysis by people who are -- most people
4 who do cost effectiveness analysis are not trained in
5 economics and traditional economic graduate programs.
6 Many of them are trained in pharmacy, doctorate programs
7 and go on to get sort of special training after that,
8 but recognizing that the way applied cost effectiveness
9 analysis is done is based on welfare maximization, as
10 opposed to sort of traditional micro economic analysis
11 which is based on total surplus.

12 Essentially one of the differences that I want
13 to draw distinction to is that applied cost
14 effectiveness analysis focuses on measuring cost
15 effectiveness across a wide set of interventions and
16 diseases and processes and looks at maximizing the
17 returns to spending an overall health budget whereas the
18 focus on surplus tends to focus within a single good,
19 and I think that's going to be a critical distinction.

20 I think there have been -- there's a few things
21 in the paper that I would encourage the authors to think
22 a little bit more about, and that is I think it's
23 written in a way that at least it seems to me that the
24 criticisms of CEA that are in there are in a sense not
25 criticizing what is actually done in cost effectiveness

1 analysis.

2 In particular, it's written in a way that seems
3 to emphasize minimization of average cost effectiveness
4 when the criteria for adoption that are used in practice
5 are based on something slightly different or incremental
6 cost effectiveness ratios, and I would like to go in to
7 a little bit more in talking about how the decision
8 rules that are based on incremental cost effectiveness
9 that are used -- how those decision rules are made, and
10 in particular what is the role for overall social
11 surplus and overall social income in setting the
12 threshold of what is considered a cost effective
13 intervention.

14 And then I would like to finally wrap up by
15 proposing that perhaps the monopoly R&D model which is
16 the basis of some of the calculation in the second half
17 of the paper maybe in future work might be looked at as
18 something that might be improved.

19 So just a brief overview of average cost
20 effectiveness versus incremental, if you just plot on
21 the X axis the value of an intervention measured in
22 terms of health H and a willingness to pay factor,
23 lambda, which monetizes the health benefit and plot that
24 against the cost of the intervention, which is the price
25 times its quantity, you could see that an intervention X

1 in terms of just average cost effectiveness maybe
2 considered preferable to Y because it would have a
3 higher consumer surplus.

4 And that's the basic foundation of this paper,
5 but in practice, generally what's considered is not
6 simply the average cost effectiveness analysis but the
7 incremental, which considers alternatives calculated as
8 the difference in cost between alternatives divided by
9 the difference in health outcomes. This is basically
10 what's done in UK through the National Institute of
11 Clinical Excellence there, and has been the recommended
12 practice guidelines from the U.S. Panel on Cost
13 Effectiveness in Health and Medicine.

14 So what that means is we need to take into
15 account the previous standards of care for the same two
16 diseases, X and Y, and instead of looking at their
17 distance from that horizontal line, looking at the
18 slopes of the lines that connect them, and in this case
19 we would prefer the -- to adopt the new technology that
20 actually has the worst cost, average cost effectiveness
21 because its incremental cost effectiveness is better, so
22 the difference in cost divided by the difference in
23 health valued outcomes for the condition Y would say
24 that we would prefer that technology over the one that
25 actually has the lower cost effectiveness in terms of

1 average rates.

2 So where does the lambda that monetizes our
3 value of health benefits come from? Generally the
4 welfare foundations of health economics in cost
5 effectiveness analysis can be traced back formally to
6 Garber and Phelps paper in Journal of Health Economics
7 in '97. A really simplified model of that is to say
8 imagine that you have a social planner who is trying to
9 maximize the total health of a population of people with
10 two conditions, X and Y, and is also trying to maximize
11 utility with respect to consumption of all other goods,
12 which is represented by putting this budget constraint
13 income minus total health expenditures.

14 The goal is to try to have -- to spend money on
15 health interventions across those two conditions so that
16 the marginal returns to utility are equalized across
17 both of those interventions or both of those disease
18 times as well as with respect to all other goods.

19 And the lambda comes in from how much money you
20 have to spend on health end total, so the concavity of
21 the utility of all other goods would imply that the
22 willingness to pay for health interventions increases as
23 your total income level increases.

24 Why that's important is because in surplus
25 appropriation models, in this framework, theoretically

1 surplus appropriations should have no role whatsoever
2 because the producer surplus is redistributed as income
3 either to individuals as shareholders or to society in
4 total. Then as social income increases with profits,
5 then the willingness to pay for health interventions
6 should also increase.

7 Finally I would just like to make a suggestion
8 that monopoly may not be the most reasonable model for
9 measuring returns to R&D, and for making the
10 calculations in the second half of the paper. Basically
11 under monopoly with barriers to entry we know demand is
12 downward slopping. That means that there is some
13 ability to withhold some supply to increase price and
14 therefore increase profits and we know that that's the
15 case in health innovations, but just how inelastic is
16 the demand? Well, when we think about health demand for
17 a specific product that doesn't tell us the entire
18 story. In the U.S. health economy in particular, and
19 throughout the world, healthcare is by and large
20 purchased by groups of individuals through risk pooling
21 methods like health insurance or by government
22 purchasers, and numerous health conditions are being
23 considered demanding possibly thousands of different
24 types of interventions, so manufacturers are not just
25 competing for expenditures within a single drug class

1 but they're really trying to grab attention for spending
2 across a whole variety of different conditions.

3 So I would suggest that maybe you might want to
4 consider monopolistic competition as an alternative
5 model. It allows for greater elasticity of demand, and
6 it also implies that we would see the things that we do
7 see in the drug market like product differentiation,
8 advertising, search costs, et cetera.

9 So I would like to thank again the authors. I
10 enjoyed reading the paper, and thanks, Chris.

11 MR. ADAMS: Thanks, David. Why don't we -- I'll
12 take one question, if there's one question for Tomas
13 quickly? No. Do you want to ask a question?

14 MR. WENDLING: Is there anyway that the cost
15 effectiveness analysis studies could address information
16 asymmetries between the producer of the goods and the
17 purchasers of the goods?

18 MR. PHILIPSON: I think of it -- as I said, I
19 think of it as regulating the price, so -- cost
20 effectiveness is given by the technology, and the only
21 thing left to regulate is the price. I don't see
22 exactly -- unless they're over, under usage by that
23 asymmetry and therefore could be counteractive that
24 might be a way, but I haven't thought about that issue.

25 As to the comment, the income effect essentially

1 that talked about in the Phelps Garber is sort of
2 demonstrating the difference between dynamic and static
3 I think. It really means who gets the surplus for
4 dynamic incentives, obviously. If you have a perfectly
5 priced discriminating monopolist, he gets the entire
6 surplus, that's equivalent to perfect competition, all
7 the surplus going to the consumer in static efficiency,
8 but it's obviously a very different implication for
9 dynamic efficiency of generating the product, so that's
10 I think the Garbler Phelps just points to what the
11 problem is, that focuses on the static as opposed to the
12 dynamic incentives.

13 In terms of the elasticity of demand through
14 monopolistic competition, it's actually interesting
15 which I didn't get to in this short time period, but it
16 turns out that more elastic the demand is, the less, so
17 that usually we think means high prices, so people are
18 dying of HIV. They're very inelastic in how -- they're
19 probably going to pay a lot for these technologies as to
20 saving their lives. Consequently the prices of these
21 technology are very high, but it turns out the more
22 inelastic demand is, the lower is appropriation.

23 Even though prices are high, we think, okay,
24 that's good news for profits, but that's bad news for
25 appropriation, and the reason is because when demand is

1 inelastic, consumer surplus many times goes up faster
2 than producer surplus with that inelasticity, so
3 basically just because you see high prices, many times
4 does not mean that you see large appropriation of the
5 return of the innovator.

6 So high profit, high prices may still lead to --
7 as this does appear to be the case in the HIV case
8 certainly, may be very consistent with low
9 appropriation.

10 MR. ADAMS: Great, thanks, Tomas. If we could
11 have a round of applause for both those papers.
12 Hopefully we have some coffee and maybe some bagels
13 left, and we'll be back here in about ten minutes.

14 (Whereupon, a brief recess was taken.)

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1 PANEL: POLICY AND NEW DRUG DEVELOPMENT

2 MODERATOR: CHRIS ADAMS, FTC BE

3 PANEL MEMBERS:

4 JOE DIMASI (Tufts CSDD)

5 UNA RYAN (AVANT Immunotherapeutics, Inc.)

6 RANDY LUTTER (FDA)

7 DAVID RIDLEY (Duke Fuqua)

8

9 MR. ADAMS: Why don't we get started on the next
10 session. THIS is a panel discussion hopefully following
11 on from the two paper presentations talking about
12 innovation, and one of the things that I think came up
13 was incentives to INNOVATE, so I have a group of
14 distinguished panelists to talk about this issue.

15 We have Joe DiMasi, who is at Tufts and Ernie
16 refers to him as the \$80 million man; Dr. Una Ryan, who
17 is the CEO of AVANT Immunotherapeutics, and we have
18 Randy Lutter, who is -- what's your title?

19 MR. RANKIN: Associate commissioner.

20 MR. ADAMS: Associate commissioner at the FDA,
21 and David -- Jack is breaking the rules by talking on
22 the phone-- David Ridley, who's in the Duke business
23 school, so with that, we'll go in the order that they're
24 listed.

25 MR. DIMASI: Thank you, Chris. I was asked to

1 give a relatively brief presentation. I'm going to
2 present some data, a little of the information 802 and
3 some alternatives out there. There has been a lot of
4 discussion in recent years about the productivity of the
5 drug industry. This is a type of chart that's
6 frequently used. Often the R&D expenditures are not
7 deflated. Here they're adjusted for inflation, and we
8 have new drug approvals against R&D expenditures.

9 One cannot infer anything precise from this, but
10 certainly suggests that resources devoted to getting new
11 drugs to market has increased substantially over time
12 because the R&D -- these are aggregate R&D, our expenses
13 which are inclusive of efforts to get new drugs
14 approved, get new drug products approved post approval,
15 that is new formulations, new indications as owner
16 indicated, new dosage forms, all of which can have some
17 significant clinical effects.

18 I think we need to be a little tempered in our
19 perspectives here. As I mentioned, there's a great deal
20 mentioned in the media and by many commentators in the
21 industry and outside of the industry in the purported
22 decline -- of the purported decline in the productivity
23 of the pharmaceutical industry.

24 Before we get too carried out, it's interesting
25 to get a little sort of historical perspective.

1 Essentially the same sort of thing was said in 1960.
2 This is from a U.S. Senate report that was the outcome
3 or was the result of the famous Kieve Oliver Harris
4 amendments that eventually led to the 1962 amendments to
5 the Food and Drug Act.

6 This appears to be at least up in the number of
7 years leading up to that Act, a decline, if you will, in
8 the output of the pharmaceutical industry. As we see
9 from the previous slide, the industry did bounce back
10 certainly in the number of new drugs and new drug
11 approvals did increase over time.

12 Here's that \$800 million figure. Let me just
13 sort of briefly mention what underlies it since it's
14 sort of often misunderstood. These figures include the
15 cost of research failures. These are the actual -- the
16 actual cash outlays in what we refer as the capitalized
17 cost, essentially a way to capture the time cost of new
18 drug development, R&D expenditures incurred, many can be
19 thought of as an investment and are incurred many years
20 before the benefits of that investment are realized.

21 So the actual average cash outlayer approved new
22 drug for the period we analyzed was 403 million, and
23 that about doubles to 802 million once you consider the
24 time cost of new drug development here. By preclinical
25 and clinical we're just sort of denoting a point of

1 demarcation in the development process, that point of
2 demarcation being the point at which human testing
3 begins on new drugs, whether that's in the U.S. or not,
4 so by preclinical we mean everything that occurs prior
5 to human testing, so it includes basic research as well
6 as what we think of as preclinical development, and the
7 clinical period includes everything that occurs after
8 the initiation of clinical testing, including
9 manufacturing R&D for the product, the production of
10 clinical supplies, in general so-called chemistry
11 manufacturing and control costs.

12 Now, Ernie mentioned what happens, a bit about
13 what happens after new drugs get approved, and some
14 important things can happen. Particularly new uses are
15 studied and obtained marketing approval.

16 People talk about the \$802 million figure, but
17 little realized is there's another figure in that paper,
18 897 million, which is meant to take into account all of
19 those R&D expenditures that occur after initial
20 marketing approval, and here we have the cash outlays
21 per approved new active ingredient at 140 million or
22 about one quarter of the total out of pocket costs once
23 we consider R&D expenditures over the full life cycle of
24 the active ingredient, so this includes all of the sort
25 of new dosage strengths, new dosage forms, new

1 indications, work that's done post approval.

2 We've done three studies in this series, going
3 back to date in the 1970s. Actually the study samples
4 are determined on the basis of when drugs enter clinical
5 testing, but you can think of them or roughly in terms
6 of when those drugs yielded approvals, and the first
7 study essentially had 1970s approval, the second 1980s
8 approval, and the most recent studies, 1990s approval,
9 although it did extend it a bit into the 2000s, and it
10 was weighted a little bit more toward the end of the
11 period.

12 The average approval date was 1997, and if you
13 use those average approval dates, you can get compounded
14 annual growth rates across the studies and so across
15 these decades, and we see very substantial increases in
16 resource costs over time even after adjusting for --
17 this is after adjusting for inflation.

18 Pretty close -- the overall growth rate is
19 pretty close for the '70s to the '80s, and from the '80s
20 to the '90s, but there was an important difference in
21 terms of the make-up of that growth. Most of the growth
22 in cost in the most recent period was accounted for by
23 growth in the costs in the clinical period.

24 This slide is here just to make everyone aware
25 that not all costs are average. Not all drugs cost the

1 same to develop. In particular you can get significant
2 variation in development cost by therapeutic category,
3 and here we have the cheapest, if you will, the
4 analgesic anesthetic class, although if we did this for
5 more -- if we did this for more recent data in going
6 forward, given the withdrawal of Vioxx, I suspect that
7 development costs may increase for the analgesic class.

8 Now, what about a set of alternative estimates?
9 Well, let me just go through these. Public Citizens
10 published on their web site in a report in 2001, later
11 amended somewhat after our figure of 802 million came
12 out, there are a variety of cost estimates in there. I
13 picked three types in their lowest forms here, 77
14 million, 150 million, 266 million.

15 One approach Public Citizen took was simply
16 ignore the time costs of new drug development and also
17 to reduce the remaining costs, the out of pocket costs,
18 the cash out base according to the average corporate
19 income tax, which they took to me -- which was 34
20 percent for the period, so the 266 million here is
21 really the 802 million with the time cost taken out and
22 multiplied then by .66.

23 I don't think -- of course it's important I
24 think to consider time costs, and their view of the
25 corporate income taxes is faulty. Instead of viewed,

1 it's sort of viewed as sort of corporate welfare there
2 in their report, and it's really a tax on profits, and
3 it's necessary to reduce revenues by costs to get the
4 appropriate base for the tax.

5 Now, there are second order issues here related
6 to the corporate income tax that could be considered,
7 R&D expenditures are investments, but for accounting
8 purposes and tax purposes they're treated as current
9 expenses when ideally they should be -- they should be
10 capitalized.

11 There are also R&D tax credits and orphan drug
12 tax credits although for the type of firms that we
13 analyze, which we analyze the pipeline as traditional
14 pharmaceutical firms, so we discussed this in our paper,
15 these tax issues, that did not seem to be perfectly
16 empirically significant based on the financial
17 statements of a number of large pharmaceutical firms.
18 That's sort of the tax credit aspect of that seemed
19 to -- savings seemed to amount to something like 2 to 3
20 percent of total expenditures.

21 I'm running a little short on time I see, so I
22 won't discuss what I think are serious flaws in the
23 Public Citizen report. We actually have a paper on my
24 center's web site detailing all those flaws. Chris
25 Adams and Van Bratner from here published a paper in

1 Health Affairs this year which used information from a
2 commercial business intelligence database to look at
3 development types of success rates and applied them to
4 our data and came up with a similar cost per approved
5 new molecular entities, 866 million.

6 The Boston Consulting Group had in 2001 done a
7 report with a figure of 880 million. Payne, the firm
8 Payne had a report which was reported to have costs of
9 1.7 billion. That needs to be clarified a bit. They
10 included 250 million in launch costs which of course we
11 do not. That brings the figure down, but also what is
12 not commonly understood is their data presumably applied
13 to, as they said, approvals from 2000 to 2002, but they
14 also had an estimate in there that is not talked about
15 very much for approvals, for drugs approved for 1995 to
16 2000 which much better fits our time period and that
17 figure -- they figure they had there was 1.4 billion.

18 And again if you take out launch costs, they
19 didn't specify them for that period, but if they're same
20 proportion as for the 2000 to 2002 period, that gets you
21 down to 933 million, and although they don't say it,
22 they were probably thinking I think in terms of current
23 dollars, 2003 dollars or 2002 dollars. If you deflate
24 then to the year 2000 dollars, which our figures are in,
25 then that gets you back into the \$800 million range

1 where the other figures are.

2 Okay. These data have been used in a number
3 of -- from these studies a number of rate of return
4 analyses, by Henry Gurbowski and John Vernon and in the
5 most recent one I joined them as a coauthor. This just
6 sort of gives you sort of the blockbuster dependence for
7 the pharmaceutical industry in recent decades. It shows
8 us the skewness of sales.

9 The results of this study showed a -- that the
10 eternal rate of return was for drugs approved, new drugs
11 approved in the early 1990s, 1990 to 1994, was very
12 close, was only sort of modestly higher than the cost of
13 capital.

14 Now, Chris, in an Email prior to the meeting,
15 raised the question about the cost of biopharmaceutical
16 or biotech drugs, if you will. Fortunately we actually
17 have some new data on that. This is from a study that
18 is going to appear in print, should appear in print
19 fairly soon. We were able to analyze data from a large
20 biotech firm and combine that with some
21 biopharmaceutical data that we had from our previous
22 study to develop estimates of the average cost of
23 developing a new biopharmaceutical, by biopharmaceutical
24 here we mean physically were common in proteins, and all
25 them antibodies which has been the dominant type of

1 biotech, if you will, drugs that have been approved,
2 that have been approved to date, and we have the out of
3 pocket or cash outlay costs here.

4 These are compared to the results from our 2003
5 study for the pharmaceutical, traditional pharmaceutical
6 industry. Those are the blue bars, and these are
7 expressed in the year 2005 dollars.

8 However, the data that we have for the
9 biopharmaceuticals are of a somewhat more recent
10 vintage. One can estimate that they are in some sense
11 five years more recent, so if we did a thought
12 experiment, and that was to take our pharma cost data
13 and adjust them upwards according to past growth rates,
14 so we took the growth rates we had from the previous
15 studies, applied them to the data that we had from our
16 R&D cost study and looked for what pharmaceutical R&D
17 costs might be if they had grown in the most recent five
18 years as they had in the previous decade.

19 And so that gives you the sign in bars, and we
20 see somewhat higher even adjusted for the time period,
21 preclinical costs, lower clinical costs and lower at
22 least relative to the time adjusted data total out of
23 pocket costs.

24 However, the biopharmaceuticals had somewhat
25 longer development times. They did have a higher

1 success rate, 30 percent relative to the 21 and a half
2 percent that we had used for the pharma study, but we
3 also had used a higher cost of capital for them, so if
4 one capitalized costs, one gets these results
5 significantly higher, 1.2 billion than the 800 million
6 that we had, 899 million in year 2005 dollars, but if
7 the pharma costs had increased in the more recent
8 five-year period as they had in the past, then you get
9 essentially the same total cost, a cost that was only --
10 the biopharmaceutical costs, only 6 percent lower than
11 the pharma time adjusted cost.

12 Now, there are certain qualifications here. One
13 of course is that we don't know the actual growth rate
14 of pharmaceutical R&D costs. That would await further
15 study, and the other is that the distributions of the
16 compounds amongst the biopharmaceuticals and that were
17 in the pipelines of the traditional pharmaceutical firms
18 of somewhat different. The biopharmaceutical compounds
19 are more concentrated in the oncology and immunology
20 area. The compounds in the traditional pharmaceutical
21 firms are more concentrated in the cardiovascular and
22 CNS area.

23 What that means is not entirely clear. For the
24 previous year, the cardiovascular and CNS drugs had
25 costs that were sort of close to average, but we didn't

1 have enough information on oncology and immunology
2 drugs.

3 (Applause.)

4 MR. ADAMS: Why don't we bring up Una Ryan to
5 talk. Dr. Ryan is CEO of ADVANT Immunotherapeutics and
6 actually lives and breathes these issues.

7 DR. RYAN: I'm delighted to be here and very
8 grateful for the invitation. Vaccine development is
9 sort of the extreme cost of drug development. Time
10 lines are longer. Margins are smaller, and the costs of
11 phase III development are much higher, and sort of like
12 extreme skiing, you're more likely to crash, but if it
13 works, it's really exhilarating.

14 Vaccines are sort of at a crossroads. The old
15 technology is giving way to new molecular immunology.
16 We understand the immune system better. We can use
17 genetic engineering rather than just crippling bugs in
18 order to make vaccines, and perhaps one of the most
19 important things is we have new markets. We have
20 markets for adults and adolescents, and the assumption
21 is that they will pay better than babies, and we have
22 therapeutic as well as preventive vaccines.

23 But it's at a crossroads because issues do
24 remain, and one of the most distressing is really the
25 irrational public fear of vaccines that I believe is

1 fanned by the media, and the fact that in many ways
2 we've all forgotten the diseases that have been cured by
3 the vaccines for childhood diseases, and so the threat
4 now is of the side effect rather than of the disease.

5 The other thing that makes it difficult, and you
6 have to be intrepid to get into the business, is we now
7 have enormous phase IIIs, which are not really defined
8 for efficacy, but they're designed statistically to rule
9 out very rare side effects which I'm not sure in a cost
10 effectiveness or any other scenario is really worth it,
11 so I'm going to talk about that will a little bit.

12 Tobacco is pass^o, and the biotech industry is
13 the new place for the plaintiff's bar to play, and so
14 freedom from liability is a big issue for us.

15 We have issues of reactogenicity to adjuvants.
16 You hear about troops not wanting shots because they get
17 sore arms, so some of the innovative ways of dealing
18 with vaccines have gotten rid of that, and of course the
19 big story is always manufacturing capacity and
20 manufacturing reliability.

21 We still have uncertain regulatory pathways.
22 You don't really know as you set down the road what size
23 of phase III you're going to have to plan for either in
24 time or money, and the reimbursement system is
25 cumbersome for the existing vaccines and in my view

1 worse for the ones that are in the pipeline.

2 However, you can reduce the big issues down to
3 three big things. The first is return on investment,
4 and I would say until now this probably hasn't been very
5 positive for firms in vaccine manufacturing.

6 Immunization for manufacturers is a big issue. It's
7 often not talked about directly, but people can be put
8 out of business, and they won't go down certain avenues
9 because of fear of litigation, and I think regulatory
10 predictability is perhaps my biggest fear in a small
11 vaccine firm.

12 Now, let me just quickly go through this stage
13 of play. I'm not going to spend a lot of time on each
14 thing, but if you look at the vaccines for children,
15 they're largely preventive. They've been highly
16 successful, but the CDC, the government is the buyer and
17 the margins are low and actually decreasing. People are
18 bidding lower.

19 We do have quite a lot of government you might
20 want to call it support. There's the VFC, the Vaccines
21 For Children's Fund, originally defined for poor
22 children, but actually now for the uninsured and
23 underinsured, which are not necessarily poor children.
24 Their plans just don't pay for immunization. We have
25 the Vaccine Adverse Event Reporting System, which is

1 good in that it does tend to reduce the liability to
2 manufacturers and so does the Victim's Vaccine Injury
3 Compensation Program. These are very helpful at present
4 they are simply for children.

5 The complex relationship between who pays for
6 immunization is very strange. The vaccines are bought
7 by the federal government. They are distributed by the
8 states, and sometimes they are paid for by insurers, and
9 some states behave better than others in terms of paying
10 for their vaccines, but there's no money for
11 infrastructure here, no money for the nurses, the
12 storage or anything. The vaccines are bought, and it's
13 up to the states to distribute them.

14 If we move now from vaccines for children to
15 vaccines for adolescents and adults, and some exciting
16 ones are coming down the pike, we find that they are to
17 treat ongoing disease as well as to prevent the threat
18 of disease, but we really have no infrastructure at all.
19 We don't have those things that started with what I
20 showed you before for adolescents and adults, and of
21 course there are social issues.

22 You've all probably heard about the vaccines for
23 human papilloma virus, which really have to be sold as
24 vaccines to prevent cancer for fear of engendering
25 thoughts that they might stimulate promiscuity.

1 Finally, we have new threats. We have pandemic
2 and deliberately emerging threats, and here the biggest
3 problem is manufacturing, how do you get enough
4 manufacturing to deal with a surge where you might need
5 to immunize massively across the country, and yet have
6 manufacturers able to keep those plants waiting in case
7 more is needed, very, very difficult problem.

8 Again we have government monopsony issues. We
9 have good new legislation for purchase commitment, but
10 we're not really sure what the price will be or how many
11 doses there will be required, very difficult to plan.

12 Immunization, we in the industry have fought
13 very hard for this. It is in place at the moment but,
14 I'm ashamed to say my home state Senator is trying to
15 undo that. I have to talk to him more. We also have a
16 big problem in that we have good funding for research.
17 We have funding for procurement, but there is what we
18 call the valley of death in between.

19 One thing is the vaccines have to go through
20 late stage clinical trials and manufacturing, huge risk,
21 huge cost, and no real government support for that but
22 new legislation might be a good start there.

23 I keep mentioning regulatory predictability and,
24 we need to understand that, one, we have dual use or
25 sometimes in the developing world as well as in the

1 developed world, we are going to have to have tiered
2 pricing, and for that patents are absolutely critical.

3 So on the regulatory side, the biggest problem
4 that I'm seeing with the vaccines that I've had to deal
5 with recently is the very large phase III safety trials
6 for Rotarisk against rotavirus infection. The trials
7 are now a little over 85,000 babies in phase III and
8 mounting. Now, I'm not sure very much what is achieved
9 with this, and I cannot see any reason why it couldn't
10 have been done better in post marketing surveillance.
11 As was mentioned this morning, that is the real
12 population.

13 Now, there's a lot of impending legislation for
14 post marketing surveillance, pharma co vigilance phase
15 IVs, but what we must have is that new legislation
16 instead of these large safety phase IIIs, not on top of
17 it. If it's another burden, I really am sure that
18 people will back out of this kind of development.

19 I think we do need to reauthorize the
20 Prescription Drug User Fee Act. Where we are now is it
21 has increased costs to the companies, hasn't really
22 shortened time lines, but as we begin to look at
23 increased industry support for the FDA, we are fueling
24 the already existent fears of industry control of the
25 regulatory agency.

1 So it's a very difficult situation. I think the
2 industry desperately wants the FDA to have more support.
3 We can understand completely that it's underfunded, and
4 while I think it's not a lack of generosity, we don't
5 want to be the ones to fund over 50 percent of the FDA,
6 and that's where the statistics come now. So I think we
7 desperately need more Congressional support for the FDA.
8 This is a very good use of government money.

9 So I think some of the solutions might be that
10 we just need to reduce the risk for vaccine development.
11 We need to be able to calculate what kind of regulation
12 we're going to need for safety and manufacturing. Even
13 if it's large, as long as we know what it is, we can
14 calculate in times and money. We can come up with MPV,
15 but right now it's pretty much a lottery. We need
16 freedom from liability, except if we screw up of course.

17 We need committed purchase for things like
18 pandemics and biodefense, but committed purchase means
19 we need to know what price per dose and how many doses
20 over time, and we need all insurers to cover
21 immunization. It's a patch work at the moment with some
22 states as I said defaulting to the Vaccine For
23 Children's Fund which was only designed for -- it's an
24 entitlement for poor children and underinsured children,
25 and we need to build the same structure for adults and

1 adolescents that we have in place for children to
2 protect manufacturers, to protect victims, to protect
3 everyone.

4 So my questions are really quite big ones. I
5 don't think that people understand the fragility of this
6 industry. People are up in arms one we don't have flu
7 vaccines when there's a measles outbreak, but very, very
8 often these are diseases that could be very easily
9 treated or prevented or reduced in numbers by vaccines,
10 but if we don't have the right regulatory environment
11 and the right business and science environment, they're
12 not going to be developed.

13 So I want to ask the big questions: Will there
14 be new vaccines? If we have them, will they be able to
15 be distributed to all people that need them? But even
16 worse, will all the people who need them actually accept
17 them and take them? And one of the questions that's
18 come up and I don't think it's hyperbole, but will it be
19 a U.S. vaccine industry? Are we going to make it
20 possible for that to exist?

21 Thank you very much.

22 (Applause.)

23 MR. ADAMS: Next we're going to have Randy
24 Lutter who is going to respond to the comments.

25 MR. LUTTER: Good morning. It's a pleasure to

1 be here. Thank you, Chris, for the opportunity, and
2 especially I'm delighted to be part such an illustrative
3 panel. Tom Philipson asked me earlier if I was
4 presenting a paper, and I said no, this is a talk. As a
5 former academic and now government, I guess bureaucrat,
6 I think it's important to make the distinction, but
7 anyway it's a pleasure to be here.

8 I would like to not respond to the earlier
9 comments or even the call to, although I don't disagree
10 with that key point about what was it, I think resources
11 and Congressional action, but I would like to talk to
12 you broadly about an FDA perspective on some issues
13 pertaining to you in drug development. There's a slide
14 here that is very similar to one that Joe DiMasi showed.
15 This is a somewhat different time period.

16 R&D spending has been growing very rapidly over
17 the last 15 years or so, and this is a pharma, and then
18 total NIH budget in blue. R&D spending is of course
19 fairly difficult to measure carefully because there's a
20 question, a variety of questions about exactly what is
21 meant by it and what is captured.

22 If you ask the productivity question, the stance
23 that HHS has taken recently on this is actually not to
24 focus on the NAD approvals or the drug approvals by FDA
25 per se, and the reason to do that is it's largely a

1 global market, and it's a global industry, and if the
2 multinational drug companies are putting resources into
3 drug development, one might ask, Well, what does that do
4 to worldwide new drugs coming out of market rather than
5 only those in the United States, and here what's
6 mentioned are new active substances, which there's a
7 broader measure than the new molecular entities or new
8 chemical entities I think that Joe DiMasi used.

9 It's from a script world, and I think it's the
10 broadest one, and what you see is a downward trend in
11 the years since the mid '80s, and what you also see is
12 that increasing share of the products which are first
13 approved in the United States, and this is a
14 modification. It's a slight update to include 2004 of
15 data published in an HHS report to Congress on drug
16 importation.

17 So what it shows is that there's a disconnect,
18 if you will, between a very large rate of growth in R&D
19 globally and a decline in new active substances approved
20 globally, even though the relative share from the U.S.
21 perspective is okay. It's been growing.

22 If you look at the data slightly differently,
23 what about new active substances first launched in world
24 markets by U.S. companies? In other words, the U.S.,
25 from looking at it from a U.S. perspective, there's

1 probably two areas that might be interesting. A company
2 may have different incentives to launch here,
3 independent of where the company is. After all, we have
4 marketing where prices aren't set by government, but
5 then the question is: What is the productivity of the
6 U.S. R&D companies? And this speaks to the NASS first
7 launched in world markets by a U.S. company, so what you
8 see is it's the share which is the U.S. has been
9 relatively stable since I guess the late '90s. There's
10 a variety of measures of FDA's impact. Some these are
11 related to the Prescription Drug User Fee Act.

12 The general theme here is the median total times
13 to approve new drugs has been falling regularly both for
14 what we term priority applications, ones expected to
15 have a significant effect on health and represent
16 improvements in existing therapies and standard
17 applications, and these are median numbers, and actually
18 the six month interval -- I'm sorry I don't have the '05
19 and I'm not sure why I don't have that, but the median
20 estimates are actually consistent now.

21 They're fully consistent with the performance
22 standards in the Prescription Drug User Fee Act, which
23 is six months and that's mind you a standard not for
24 approval. It is a standard not for a final decision.
25 It is a standard for a decision, so if the application

1 is ill prepared, then it can cycle back again, and it
2 doesn't require us of course to approve the drug. It
3 merely requires a decision within six months, but the
4 decisions nonetheless that the median approval time ends
5 up being six months.

6 I wanted to comment briefly on the 802. I think
7 Chris asked me for some thoughts on that, and since Joe
8 is here, it seemed appropriate. That's a very well
9 accepted number for a variety of sources, and I think in
10 that sense it's a fairly significant accomplishment,
11 that probably the -- I think Joe did not mention that it
12 was referenced in a GAO study I believe in the late '90s
13 as representing a credible estimate, so notwithstanding
14 the controversy associated with it, it's been used in a
15 variety of ways.

16 There's an HHS report to Congress that mentions
17 a few caveats pertaining to it that I thought I would
18 just throw out to put it in perspective. Very broadly
19 one might ask, What exactly is a drug, and if you say
20 \$802 million per drug, what exactly do you mean? And
21 already there has been several definitions here.

22 I think what the report is investigational self
23 originated therapeutic. The HHS task force mentions a
24 couple other points on it, and that is that it applies
25 only to self originated new drugs marketed by large

1 multinational pharmaceutical companies. There's a sense
2 in which outsourcing may lower the costs by an unknown
3 amount.

4 I think it also neglected biologics, and in that
5 sense it doesn't necessarily apply to all drugs approved
6 by FDA, and many of the kinds of compounds excluded from
7 the analysis are orphan drugs, which may be developed by
8 relatively small entities and therefore arguably have
9 lower costs associated with them, but the key messages
10 of that report is that it is credible enough to provide
11 useful insights.

12 I thought what was also interesting is there's a
13 recent CVO study that came out in October of 2006 that
14 also shares what I thought was a key theme of Joe
15 DiMasi's work, and that is the increase in the cost over
16 time, and what's remarkable is that that 7.7 percent, if
17 I recall, which applied to his two earlier papers, if
18 extrapolated into recent years, would lead to a
19 significantly higher number than the 802 because the
20 drugs approved in the paper that generated the 802
21 million I think had a median approval date of 1997 which
22 is already nine years ago.

23 A couple comments on FDA's involvement on the
24 cost of drug development. If you think about what the
25 future might bring and how the past debate has been

1 shaped, there's a key distinction to be made between
2 accelerating review times and other involvement in the
3 development process, and currently I showed you a couple
4 slides back that the review times are already relatively
5 short, okay.

6 So you might think, Well, if you had here a very
7 radical reduction in the review time, say from six
8 months to say four months, that's a monumental change,
9 right, of 33 percent. Many people would think that's
10 completely infeasible. What does that really get you
11 overall? Well, not very much, and the reason is that
12 you're talking about 10 or 12 years on average between
13 discovery and patenting of the molecule and actual
14 marketing, so a reduction of two months is relatively
15 inconsequential even though that would be very, very
16 costly from a review perspective per se.

17 Therefore, the real question is: What can you
18 do to facilitate and accelerate the development in other
19 stages of the process? And you can think of those as
20 the phase I, the phase II, the phase III trials. We
21 have one initiative which was actually launched by Mark
22 McClellan when he was commissioner of FDA, and it's
23 called the critical patent initiative.

24 We have I think the President's budget request,
25 which is currently under review in Congress which asks

1 for I believe \$6 million for this so in that sense it's
2 still a relatively small initiative. We have a
3 consortium set up with substantial industry funding
4 through academic institution in Arizona and a couple of
5 others in play. The basic idea is to develop, if you
6 will, improved science on the predictability of drug
7 development, and you can think of this as since all of
8 the revolutionary work on the human genome over the last
9 ten years, there's generally little direct effect on
10 predicting or use of that on predicting basic issues
11 like toxicity of new moleculars or expected
12 effectiveness and how those might vary in patient
13 populations.

14 But applications of that genetic information to
15 improving the predictability of toxicity, meaning safety
16 or efficacy, could have huge implications both on the
17 time required to develop new products, the complicity
18 and size of the trials and ultimately on the medical use
19 themselves.

20 I'm reminded a little bit -- I'm running out of
21 time. Let me skip to the last point.

22 We have one analysis which is not yet out
23 formally but we can talk a little bit about the
24 implication of it because it deals with a very widely
25 used drug thinner, and this gives you some idea of what

1 might be forthcoming through the result of these
2 critical patent type efforts.

3 Wafarin is a very widely used blood thinner that
4 helps to reduce blood clots, and it has a very narrow
5 therapeutic range, which means if you're overdosed, it
6 induces internal hemorrhaging, and if you're underdosed,
7 you can run a significant risk of stroke, and therefore
8 finding the right dose is very tricky.

9 Furthermore, people are divided according to the
10 genetic variability, so the current therapy is a doctor
11 says, Well, I don't know whether you deserve the high
12 dose or the low dose because I don't know your gene, so
13 what I'm going to do is treat you with a median dose,
14 and then depending on how you react I'll figure it out
15 over the next month. That's current medical practice.
16 You can imagine that that leads to a very large number
17 of cases of internal hemorrhaging and of stroke.

18 The question is: How do you get the medical
19 profession to change? And the answer is you conduct a
20 trial that shows how people respond using the genetic
21 information in the course of Wafarin therapy and even
22 then you change the label. Why? Because the label,
23 which FDA regulates, is the way to articulate to doctors
24 the way in which to use the genetic information in the
25 course of medical treatment, but there's therefore a key

1 role for FDA in integrating the use of genetic
2 information in medical treatment in labeling, and that's
3 an illustration in the critical patent mission, so thank
4 you very much.

5 (Applause.)

6 MR. ADAMS: Last but certainly not least we have
7 David Ridley from Duke University to wrap it up and give
8 his thought from the academic.

9 MR. RIDLEY: Thank you. Chris gave us a great
10 list of questions. One of the questions was: Is Joe
11 DiMasi really the \$802 Million Man? I do have a
12 presentation, and I won't try to answer that. I think
13 you're tremendously valuable, Joe.

14 I'll try to address a couple other questions.
15 One of the questions that Chris asked was about
16 incentives for vaccines and incentives for neglected
17 diseases, and I believe Michael Kremer will probably
18 give was nice talk at lunch about incentives for
19 neglected diseases. I'll touch on that a bit.

20 We have a need for developing drugs for
21 developing countries I'll talk about briefly, and Chris
22 also asked us about what the market for generic
23 biologics might looking like, and I'll talk about that
24 briefly as well.

25 So first of all, we see neglected diseases here

1 in the middle. Just in general, limited private
2 financial incentives for orphan diseases, neglected
3 diseases, diseases of bioterrorism. When we talk about
4 orphan diseases, we're talking about diseases for which
5 there are 200,000 or fewer people in the U.S. suffering
6 from them, but many of these people have some money.
7 They have some good insurance, and so the problem is
8 there aren't enough of them in the U.S. even though they
9 might be affluent, and so we have the Orphan Disease Act
10 to address this problem.

11 For neglected diseases, there's a lot of people
12 suffering from these diseases, malaria, tuberculosis,
13 but they don't have much money, so there's not much
14 private incentive here, and then finally diseases of
15 bioterrorism. The problem is that you're unlikely to
16 need the treatment, and if you do need the treatment,
17 the government is really not going to want to pay for it
18 at that point. They're going to want to you to give it
19 away at that point, so problems for incentives for these
20 various issues.

21 There have been some good proposals and good
22 mechanisms put in place, so there's been a lot of effort
23 on the push side so funding for research and
24 development, either with tax credits like in the Orphan
25 Disease Act, or with some donations, and Michael Kremer

1 I hope will have a chance to talk about the advanced
2 markets proposal, which is well along, very important
3 looking at malaria, tuberculosis, HIV AIDS.

4 This is a price subsidy, so it's a prizes -- and
5 they want other kinds or really different kinds of
6 different types of prizes. So push mechanisms, money
7 for R&D, meaning inputs or pull mechanisms money for
8 outputs.

9 One of the prizes that's proposed is if you
10 bring to market a drug for neglected disease, you get a
11 prize for a different drug, that's a longer patent. The
12 generic industry hates that proposal because they don't
13 want to delay coming on to the market, and there's some
14 that say you really shouldn't be subsidizing neglected
15 diseases by making some people wait longer that have a
16 given disease, so we thought a decent idea might be,
17 instead of giving somebody longer on the market, let
18 them come to market faster, so we have a priority review
19 voucher proposal.

20 So if you bring to market a drug for gangrene,
21 traumatonesis, you get priority review at FDA and Randy
22 Lutter mentioned that briefly. He compared priority
23 versus standard review. If we look at new molecular
24 entities, we're looking at median time from about 18
25 months to six months. That's about a year which could

1 be very valuable for some.

2 Joe DiMasi put up a slide that showed how skewed
3 the returns to R&D are. If we talk about that top ten
4 decile for those drugs coming to market a year sooner is
5 worth about \$350 million, and it actually brings to
6 market the generic faster too potentially because the
7 branded firm is getting back extra time on its patent
8 from being slowed down at FDA, and if it goes faster
9 through FDA. Then the generics come to market sooner,
10 but the branded manufacturer likes that. They want a
11 dollar now rather than a dollar later. Then on to --
12 I'm sure you all understand that and have no questions,
13 so on to the next paper.

14 Generic biologics: We're going to hear more
15 about biotech later on this afternoon, but pharma versus
16 biotech, very briefly, Viagra is easy to characterize.
17 Receptin is not easy to characterize, so if you want to
18 come along and make a generic version of this Viagra,
19 you say, Look, my generic looks like that. It's tougher
20 to say you look like this if you're talking about a
21 biologic, and it's tougher to replicate that process.

22 So the question is about generic biologics,
23 well, lots of questions, what should the law look like
24 in terms of our health concerns? Can we trust that the
25 generic biologic is the same as the branded biologic?

1 Do we need some clinical trials to prove that it's the
2 same stuff? So maybe -- even though it's a generic,
3 maybe we need some clinical trials.

4 So this hasn't been an issue much in previous
5 years. It's become a big issue this year for several
6 reasons. One, you start to see some blockbuster
7 biologics coming close to patent expiration. Four
8 governors said FDA you have -- FDA and Congress, you
9 have to tell us what generic biologics are going to look
10 like because it's going to save us a lot of money if we
11 can get generic biologics.

12 But we don't really have a law yet. We need
13 one. Waxman, Schumer and Clinton have a proposal, so
14 the legal question: What should the law be? Health
15 question: Do you need to have clinical trials?
16 Economic question: Does generic mean cheap?

17 Those four governors think generics means cheap,
18 so we look at this in this paper, so the generic price
19 is cheap, is low relative to the branded price if you
20 get lots of competition, but if you don't get lots of
21 competition, the generic price doesn't fall that much.

22 So we examine this. We take a theoretical model
23 of what the generic biologic market might look like, and
24 then we combine that with some data on pharmaceutical
25 generics.

1 So I'll come over here this time. The solid
2 line is generic pharmaceuticals, and this is just an
3 illustration that you get more generic manufacturers in
4 a market that expect to be big, and by big I mean what
5 the branded market looked like before patent expiration,
6 so if the branded market was big, more generic
7 pharmaceutical manufacturers come in.

8 Then we tried to think, we did an elasticity and
9 entry as the function of fixed cost. We said: What if
10 fixed costs are higher for generic biologics? They
11 might be higher because this stuff is harder to make.
12 They might be higher because you have to actually do
13 clinical trials for generic biologics whereas you don't
14 for generic pharmaceuticals really. So we said, How
15 responsive is entry going to be to increase in fixed
16 cost?

17 So we modeled that, and here you just get a
18 rough guess. You see just -- you get less entry for a
19 given market size because fixed costs are higher, and
20 then we also look at the relationship between the
21 generic price to the branded price. This is the branded
22 price before patent expiration, so how much lower is the
23 generic price than the branded price, and the solid line
24 is for the pharmaceuticals. We use data on generic
25 pharmaceuticals from the 1990s, and you see with bigger

1 market sizes, you get more entry, and you get lower
2 prices.

3 Then we said, what might that look like for
4 generic biologics if this fixed costs are higher? And
5 you can see you get higher prices, so, for example, a
6 half a billion dollars market, generic pharmaceuticals,
7 the price may be 40 percent of the of the branded price,
8 but generic biologics, the price might be 80 percent of
9 the branded price.

10 So this is just a cautionary tale. Generics --
11 we often think generic means cheap. It's only cheap if
12 we have competition driving down those prices. We might
13 have less competition, at least in the short run. In
14 the long run it could be a different picture, but at
15 least in the short run we shouldn't expect huge savings
16 from generic biologics

17 So in conclusion, neglected diseases, we need
18 push and pull mechanisms. We think our proposal might
19 be a viable complement to other proposals. Michael
20 Kremer -- I shouldn't say just Michael Kremer, there's
21 great activity in this area from many in this room, has
22 an important proposal especially targeting malaria,
23 tuberculosis, HIV AIDS. We have some suggestions for
24 price for other diseases and just a cautionary tale
25 about what generic biologics might look like.

1 (Applause).

2 MR. ADAMS: So I'm hoping that Michael can be
3 here. He will be -- oh, good. The issue, it turns out
4 that the Gates Foundation has more pull than the Federal
5 Trade Commission so that's where he is at the moment,
6 but I'm told he should have finished his meeting by now.

7 I'm going to take an opportunity as the
8 moderator in this session to ask a question: Do we have
9 David Austin here? Dave Austin, so I'm going to pick on
10 David. David just came out with a CVO report on the
11 pharmaceutical industry and R&D in the industry, and one
12 of the things he says in the report is that -- this is a
13 CVO study so there's lots of mays and if or well, we
14 don't know, but one of the thing that he says is maybe
15 the prices for drugs are not really giving the
16 appropriate incentives.

17 And so I was going to ask the panel if they had
18 a thought on this that the way the price mechanism works
19 in this industry is very complicated, and is it
20 providing the appropriate incentives so we get sort of
21 optimal drugs coming to market.

22 So if anybody wants to respond to that.

23 MR. RIDLEY: I think it's certainly true that we
24 need more and better information about the
25 characteristics of drugs that have been approved in the

1 marketplace, and in the sense that -- to the extent that
2 the information is poor, then the incentives to develop
3 drugs of certain types and with certain characteristics
4 can be distorted to some extent, so I think ideally if
5 we can get more and better information about the
6 characteristics of drugs, we can -- maybe somewhat
7 controversial about how you can go about doing that, but
8 putting that aside if we can, at least this theory we
9 can provide more appropriate incentives to develop new
10 drugs.

11 MR. ADAMS: Does anybody else want to jump in
12 there?

13 DR. RYAN: I think that the incentives aren't
14 there necessarily for vaccines, but I'm not sure it's
15 just about pricing. It's more about certainty or
16 predictability. I think that's what is so difficult
17 when you can't make the calculation ten years earlier
18 about what the market is going to look like, you can't
19 decide whether to take on the risk or not.

20 MR. ADAMS: Well, why don't we open it up to
21 questions. Scott Stern has a question.

22 MR. STERN: So I mean, I guess I was kind of
23 maybe building on Chris's comments. I was surprised
24 that there was very little discussion in the panel and
25 even in the morning to a certain extent about the fact

1 that there's a global -- in other words, we're
2 developing drugs. There's a regulatory process in the
3 U.S. but there's a global industry, and there's both a
4 comparative institutional analysis on how is the U.S.
5 doing relative to regulatory systems outside the U.S.

6 And Tomas talked about that a little bit this
7 morning, and then the second part of that is, when we
8 think about the incentives for innovation, in some sense
9 how is the U.S. -- in some sense, is -- when we consider
10 developed countries do, we see some kind of -- are
11 people able to kind of take advantage of the fact
12 that -- of the sort of a global market for a potential
13 R&D innovation in this industry?

14 MR. LUTTER: I'm not sure who the question is
15 directed to, but I guess I can try to answer a little
16 bit. We're very sensitive to it being a global market.
17 The second or third slide that I presented has the new
18 active substances approved worldwide, and shows that the
19 share approved in the United States is rising, while the
20 numbers approved globally is falling, and that's
21 actually very suggestive of the relative strengthening
22 of the U.S. industry relative to other areas
23 particularly probably the EU.

24 And I think that's consistent first with an
25 interpretation that the Prescription Drug User Fee Act,

1 broadly speaking since '92 has been a notable success.
2 In exchange for additional resources from industry,
3 we've accepted performance standards that have -- and
4 have been able to significantly accelerate review time
5 so that we're now the country that attracts the first
6 launches more than anywhere else.

7 I think on the supply side, you have to look
8 probably at NIH first, and there's no European
9 equivalent for that so in that sense even though there's
10 a global issue between R&D spending and its
11 productivity, relatively speaking in the United States
12 we're better off than elsewhere.

13 MR. ADAMS: Why don't we have one more question
14 if there is one. It looks like Dave wants to respond to
15 me. I'll give you my microphone.

16 MR. AUSTIN: David Austin from the Congressional
17 budget office. So one of Randy's slides showed a
18 graphic in the new CVO study that reported the numbers,
19 if you will, over time. Now, our take on the \$800
20 million, there's obviously a big exogenous element to
21 the increase in R&D costs over time, clinical trials
22 have been growing in size but there's an endogenous
23 element too that people don't tend to talk about.

24 We tried to give a sense of that in the study,
25 but one thing I never really got clear on was what are

1 the sources of endogenous increases in R&D costs? I
2 mean, so firms are choosing the drugs they study, and
3 the market is obviously supporting expensive R&D so
4 there's a sense in which firms are going for expensive
5 drugs because they know they can recoup.

6 I don't have a sense though for instance how
7 much control firms have over clinical trial size or
8 other possible elements of R&D costs and I wonder if
9 anybody on the panel has some insights in ways in which
10 firms could reduce those R&D costs if they had to.

11 MR. ADAMS: I think you're up, Joe.

12 MR. DIMASI: Well, I certainly think we would
13 want to, and obviously there's an economic incentive for
14 them to do that, and if you certainly observe what's
15 going on in the last say decade or so in terms of
16 conferences designed for a marketer to industry managers
17 on, really there is sort of a way to micro manage the
18 process so that you can in some sense make it more
19 efficient. You can reduce costs, reduce development
20 times, make better decisions, and that certainly speaks
21 to the fact that they would like to do that.

22 It's obviously been I think very difficult for
23 them to do that, so I mean, I guess in some sense that
24 goes to your question of sort of how much control they
25 have.

1 However, maybe Randy can speak to this. There's
2 at least reason to -- here with the FDA's credible
3 patent initiative which in some basic sense is designed
4 to make the development process more efficient. I don't
5 know if you have anything.

6 MR. ADAMS: You get to make the --

7 DR. RYAN: I think there are an enormous number
8 of ways that it can be made more efficient. I mentioned
9 one, which is if one could monitor in phase IV all post
10 marketing and get rid of some of these very, very large
11 phase III safety trials prior to market, that would be
12 enormously useful, but the other is there's still a lot
13 of repetition as you go through phase Is, probably
14 several phase IIs, and at least a couple phase IIIs,
15 you're doing reiterations so again I think if you could
16 take safety from a phase II perhaps or efficacy from one
17 and carry over to the next trial, that would be a
18 savings.

19 And while the FDA is the gold standard, there
20 are many other countries. You know, we make vaccines
21 for travelers that also have a global health use, and
22 many other countries won't accept what the FDA considers
23 enough for us to market to healthy, wealthy Americans as
24 sufficient for treating people in areas where the
25 diseases are even dim pick.

1 Again if there could be more, I don't want to
2 use the word harmonization, but sharing of the
3 regulatory requirements from one country to another, I
4 think it could save enormously.

5 MR. ADAMS: Just quickly, Randy, do you want to
6 jump in?

7 MR. LUTTER: Thank you. A couple brief
8 comments. I think what's being asked is how much of the
9 increasing trial size and complexity is attributable to
10 FDA policy changes on the one hand versus industry need
11 for greater protection, for example, from liability on
12 the other. The phase III trials may not be conducted
13 solely for efficacy. They may be conducted for improved
14 safety because it helps you out on the liability side.

15 And that has nothing to do with the an FDA
16 policy question. We would love to look at this sort of
17 thing internally, and in fact we had some internal
18 discussions about doing exactly that. We gave it up
19 because essentially it's impossible. It broke down at
20 the point of asking, Okay, let's look at the minutes of
21 meetings where people are coming in pre NAD and saying,
22 Yeah, we're thinking of this trial for phase III, and
23 would like to discuss with you its features and then
24 there's a back and forth.

25 And at what point is the suggestion ours and at

1 what point is it theirs? We figured out it was
2 impossible, couldn't conduct it, so I think officially
3 it's very difficult to say none of it is ours, but we
4 also don't have any really good handle on how much of
5 that increase in trial size or complicity may be a
6 consequence, either be endogenous in the way David is
7 using it or attributable to regulatory action.

8 But having said that, we are undertaking a lot
9 of initiatives to make the process much more efficient
10 than it used to be, and in the context of discussions
11 with industry, I think we're up to something like 7
12 meetings a day for all of the Center For Drugs. They're
13 called -- they're not -- which help sponsors come in and
14 figure out what are our needs for drug approval, and
15 these are not meeting with you and me and a couple
16 folks.

17 These are big interdisciplinary professional
18 meetings often with dozen of people from the sponsor and
19 from different teams within the Center For Drugs
20 discussing what are the criteria for approval, and in
21 that sense there's a huge effort underway to try and
22 facilitate those development efforts precisely because
23 of our concern that they may inadvertently hinder
24 development, and thereby frustrate our goal of promoting
25 public health in addition to protecting it.

1 MR. ADAMS: Why don't we stop with the
2 discussion of life saving medicine and getting that
3 quicker to market and move to more important things on
4 where is lunch?

5 If you've ordered lunch, your name and lunch box
6 should be out there. Let's meet back here in 10
7 minutes, 10:05, and we'll have Michael Kremer who has
8 walked in the room to come and present.

9 (Whereupon, a brief recess was taken.)

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1 AFTERNOON SESSION

2 (12:00 p.m.)

3 MR. BERNDT: Thank you. Within the economic
4 policy and academic research communities in recent
5 years, one of the most vibrant areas of intense research
6 interest measured perhaps by proportion of graduate
7 students who do their dissertations in this field has
8 been the interactions among economic development,
9 education and health, and Michael Kremer is one of the
10 undisputed leaders in this area.

11 Following his undergraduate studies at Harvard,
12 Michael enlisted in the Peace Corps, served as a teacher
13 in Kenya, where he contracted a relatively rare tropical
14 disease. This experience contributed to his becoming
15 professionally very interested in incentives for firms
16 to invest in R&D for treatment of neglected diseases,
17 particularly neglected third world diseases.

18 That also then spawned his much more general
19 interest in the economics of vaccines, which now
20 encompasses much more than just vaccines to treat third
21 world diseases.

22 After his Peace Corps stint, Michael returned to
23 Harvard to finish his Ph.D. in economics. He then came
24 to MIT where I had the pleasure of being one of his
25 colleagues for a number of years. Regrettably, several

1 years later, we at MIT lost Michael, and he went to
2 Harvard where he's now the Gates Distinguished Professor
3 of Developing Societies. Nonetheless, we're very
4 fortunate to have Michael in our larger community.
5 Indeed many of us have done joint research with him, and
6 today Michael will focus on the economics of vaccine
7 markets.

8 Michael?

9 (Applause.)

10 MR. KREMER: Thanks very much, Ernie.

11 What I would like to talk about today is first
12 about R&D incentives beyond patents, and then second, if
13 we are going to think about creating incentives beyond
14 those existing in the patent system, how should those be
15 targeted; which diseases, vaccines versus drugs, and for
16 that, I would like to talk a bit about where the gap
17 between private and social R&D incentives is largest.

18 So there I'll talk about a couple of different
19 pieces of joint research; first some work on incentives
20 to invest in vaccines versus drugs, which was joint with
21 Chris Snyder at Dartmouth, and also thinking about how
22 the difference between private and social incentives
23 depends on externalities from the disease, and this is
24 very much following on the work of Philipson and others.

25 So for diseases that are prevalent in rich

1 countries, pharmaceutical R&D is financed by a
2 combination. On the one hand, push, so for example the
3 NIH funded, and on the other hand -- that's direct up
4 front funding for research, and on the other hand pull,
5 market incentives to produce a product that will
6 actually sell.

7 For diseases concentrated in poor countries,
8 there's been increasing efforts in recent years to
9 create some push funding, so for example, the Malaria
10 Vaccine Initiative, the International Aids Vaccine
11 Initiative, and similar initiatives for tuberculosis,
12 for a number of other diseases, but the big problem is
13 the big pull component is missing, and there's been a
14 number of proposals to try to create that pull.

15 So, for example, there's been a discussion of
16 patent buy out, of prizes, of patent extensions so that
17 if somebody came up with the malaria vaccine, maybe they
18 could extend their patent on blockbuster drug for a year
19 or two, fast track regulatory approval.

20 One particular approach that I've done some work
21 on and Ernie has made a tremendous contribution to is
22 advanced market commitments, so I have a book with
23 Rachel Glennerster on this issue called Strong Medicine.
24 Center For Global Development had produced a report
25 which Ernie and many others worked on, which talks about

1 how that could be done practically, and I'll explain
2 what it is in a second, and this has attracted some
3 political interest.

4 So Gordon Brown, the English finance minister,
5 the British UK finance minister and probably the next
6 Prime Minister, said that the UK should do this for
7 malaria, should make a commitment that if a malaria
8 vaccine is developed, that the UK would help finance the
9 purchase of the vaccine if another rich country has
10 joined in, and he made similar statements for AIDS, not
11 quite as strong, but there's been some discussion of
12 this in the G-8, and so that one has sort of entered the
13 policy agenda.

14 What's the idea? Well, the basic idea is that
15 the sponsors of a commitment of this type would commit
16 to fully or partially finance purchases of qualifying
17 vaccines for poor countries at some pre specified price,
18 up to some fixed number of individuals immunized, so,
19 for example, suppose this were done for malaria or for
20 AIDS.

21 If a vaccine were developed and met sort of
22 technical standards, technical specifications, poor
23 countries could decide whether they wanted to purchase
24 the vaccine. There would be some relatively low price.
25 I'll just put this up for the sake of concreteness.

1 That's not necessarily exactly the appropriate price,
2 and then the sponsors would top up that price.

3 So the idea of this is this would simultaneously
4 provide R&D incentives to create an incentive for
5 biotech firms, pharma firms to start working on this if
6 they knew there would be a market for their product, and
7 it would also address the access issue.

8 There's a huge problem of once products are
9 developed, they don't always reach people in the poorest
10 countries. For vaccines there's often a 10 or 15 year
11 lag until products are getting to the poorest countries,
12 and millions of lives could be lost in the meantime, so
13 it does these in a complimentary way, so often the
14 public debate very much pitches access and incentives
15 against each other.

16 Think about the debate over AIDS drugs pricing,
17 for example. So I think that can be a very unfortunate
18 aspect of that debate. This would address both. The
19 other advantage of this is that no public money is spent
20 at least for this. Obviously push, where you drew out
21 funding, still needs to be very much a part of the
22 picture, but no money is spent if no vaccine is
23 developed, so this is very results oriented, and it's
24 very market oriented because firms are making the micro
25 decisions about which technologies to invest in. It's

1 not sort of centrally managed. That's the principle of
2 the purchase.

3 Let me show you a little bit of what the time
4 line might look like for something like this. So what
5 the Center for Global Development reported is that there
6 would be two steps of this. First there would be some
7 framework agreement, which the sponsors would set forth
8 which would sort of set out what the specifications
9 would be, et cetera. Companies could then sign up to
10 this.

11 The contract at that point would be binding on
12 the sponsors. Sponsors would say we'll help immunize
13 300 million people at 15 cents each, and then they're
14 obligated to do that, and the firms can decide whether
15 they stay in or out, depending on how technology is
16 going. They might have to report periodically.

17 There would be an adjudication -- so when the
18 framework agreement was announced, there would be
19 certain specifications set forth, but to determine
20 whether a product actually met those specifications,
21 there would have to be some sort of independent
22 adjudication commission to determine whether the
23 specifications had been met. There would be
24 opportunities for firms to talk to that, just like they
25 could talk to the FDA now.

1 So if the vaccine were approved, then the
2 developer of the vaccine would enter into a guarantee
3 agreement, the terms of which would be set forth
4 initially, that would involve a price guarantee, and
5 then they could install manufacturing capacity. In fact
6 they could in fact start installing that earlier the
7 specification of that. There would be procedures for
8 adverse event reporting and so on.

9 Then what the Center for Global Development
10 report envisioned was that this would not be a
11 commitment to only buy the first product that was
12 developed, but in fact if additional products were
13 developed and if they were superiors, firm, countries
14 could decide to buy those, but suppose that a superior
15 vaccine were developed, then that could be purchased.

16 Until eventually the commitment, for example,
17 that a certain number of people immunized were
18 exhausted, at that point, if the firm had received
19 enough payments under the system, they would be
20 obligated under the agreement to provide vaccines to
21 countries at some agreed on price designed to cover
22 marginal costs.

23 So the basic idea of this is that it's a two
24 part pricing for economists. The idea is to have some
25 market so over some period, firms would receive a

1 relatively high price, but then thereafter, pricing
2 would be at a lower price, somewhat above marginal cost,
3 and then that would help address this access problem
4 while creating incentives.

5 So one of the very interesting issues from an
6 economic theory point of view is how should this be
7 structured in terms of the incentives for the first
8 developer versus subsequent developers perhaps of a
9 superior product? Clearly there are trade-offs here.
10 There are advantages to both create guarantee in some
11 market for the first developer and there are advantages
12 to creating incentives for improvement.

13 The trade-off that the working group established
14 by the Center for Global Development came up with was to
15 not have a particular quantity guarantee for the first
16 mover, but instead to really have a market, but a market
17 among the qualifying products. So the idea would be
18 that a product would qualify either if it was first or
19 if it was subsequent and it was technically superior at
20 least in some way, so that creates incentives to
21 innovate and to invest, to do so quickly, but also to
22 develop second generation products.

23 This also, having some triggers so that the
24 developing countries have to be willing to use this
25 product, either they or donors acting on their behalf

1 have to be willing to put up at least something ex-post
2 creates an incentive to develop a product that not only
3 meets the technical specifications but something that
4 developing countries are actually going to want to use
5 because it would be very politically embarrassing and a
6 waste of money if you wound up being legally obligated
7 to pay for something that no country would be willing to
8 use.

9 So the firms would still face some demand risk.
10 The idea here is not to completely eliminate the demand
11 risk, but rather to eliminate that component of the
12 demand risk which is really the political risk, the hold
13 up risk that you develop a product which is perfectly
14 good, but then you face intense political pressure to
15 sell it at very low prices because the country would be
16 able to buy it at low prices, but the sponsors would be
17 obligated to top that up.

18 So some rough calculations suggest this would be
19 very cost effective, so this is some work with Ernie and
20 with others. A rough calculation is the commitment of
21 \$15 each for each of the first 200 million doses would
22 generate a market that's comparable to the market for a
23 lot of existing products in terms of the net present
24 value. It would be very cost effective from a public
25 health perspective, so it would cost about \$15 per

1 disability adjusted life year saved.

2 So in comparison, figures of 50,000 or 100,000
3 per disability adjusted life year are not uncommon for
4 developed countries, but even in developing countries,
5 you get numbers like the value of the country's annual
6 GDP per capita, or if you want to be conservative, a
7 hundred dollars as a cut off for effectiveness. This is
8 extraordinarily cost effective, and that seems to be
9 fairly robust through a variety of scenarios, and in
10 this article, we have links to spreadsheets on the web,
11 and you can play around with it and look at various
12 scenarios.

13 We wanted or we thought it would be useful to
14 have some specificity so we put down numbers for a
15 particular scenario, but obviously you could play around
16 with the scenario of how this is set up, so that's
17 summarized in the article with Ernie.

18 So suppose you're interested in this approach or
19 suppose more broadly that you're interested in some
20 other approach to supplement patent incentives, so that
21 could be other pull mechanisms like patent extensions or
22 it could be just push funding of the sort that we
23 already do for rich country diseases and is increasingly
24 being done for diseases of poor countries.

25 If you're allocating public resources for R&D,

1 you need to know when there's going to be a large
2 discrepancy between private and social returns, to think
3 about where should the resources be targeted, and I
4 wanted to talk about some research that I'm doing with
5 Chris and with Heidi Williams, with Chris Snyder of
6 Dartmouth and with Heidi Williams, who is a graduate
7 student at Harvard, about what are some particular areas
8 where there's likely to be a very large discrepancy.

9 First let me talk about some work with Chris
10 Snyder. The basic idea of that work is if consumers are
11 heterogenous, it's often possible to extract more
12 revenue as a drug producer than as a vaccine producer,
13 so here's the logic, and you often hear this. I mean,
14 there's a sort of conventional wisdom that --
15 conventional to everybody but economists that drugs are
16 more profitable than vaccines, and to economists, that
17 seems a little bit mysterious, so here's a scenario
18 under which with sort of very standard economic
19 reasoning, that might be the case, for diseases where
20 consumers are very heterogenous and risk of infection.

21 So imagine, here's a cooked up example, but to
22 show the idea, suppose there are a hundred consumers out
23 there. Suppose there's a low risk class. 90 of them
24 have a 10 percent chance of contracting the disease, and
25 there's a high risk class so ten of them have 100

1 percent chance of contracting the disease.

2 Well, suppose this is a disease that people are
3 willing to pay a hundred dollars to avoid, and suppose
4 everyone's risk neutral. Then if you're a producer,
5 suppose you're a vaccine producer, you have two
6 marketing strategies. You could charge a hundred
7 dollars and sell to the high risks only. Then your
8 total revenue is going to be a thousand dollars.

9 Alternatively, you could charge \$10, which is
10 the reservation price at the low risk consumers, and
11 then you will sell to everybody, and you will also get a
12 thousand dollars, a hundred times ten.

13 On the other hand, if you produce a drug, then
14 we can go back to the set up, while you'll sell to
15 all -- and you can sell your drug for a hundred dollars,
16 the price people are willing to pay in order to avoid
17 the disease, you sell to all the ten high risk
18 consumers, and then on average you'll sell to nine of
19 these, so you'll get 19 sales at a hundred dollars each.
20 You make 1,900, so the drug producer is effectively able
21 to extract the full consumer surplus whereas the vaccine
22 producer is only able to extract half of them.

23 So obviously in this case, will that produce a
24 distortion on incentives? Well, in the above example,
25 maybe socially it doesn't matter if you produce a

1 vaccine or a drug, but you can imagine in a case if the
2 efficacy of the drug or the vaccine were less than 100
3 percent, it would make a difference, and there would be
4 a distortion.

5 So Chris and I tried to explore this further,
6 and we said, Well, what do you need to get results like
7 this? In some way this example is very cooked up. You
8 have a very small high risk group, and you have a very
9 large low risk group. It turns out that when you get a
10 very big discrepancy between social and private value is
11 exactly when you have that sort of relationship, when
12 you have a very skewed distribution of risk.

13 If you think about the diseases where you have a
14 skewed distribution of risk, sexually transmitted
15 diseases tend to fall into that category. If you look
16 at distributions of number of sex partners, for example,
17 they're very skewed. Most people have a very few
18 partners. Some people have lots of partners, and you
19 then can add in things like particular sexual practices
20 or IV drug use, and those probably make it still further
21 skewed.

22 So when we calibrated this, the estimated gap
23 between drug and vaccine revenue can be up to four fold.
24 We did some empirical work suggesting that vaccines are
25 significantly less likely and drugs are more likely to

1 be developed for sexually transmitted versus non
2 sexually transmitted diseases, so that suggests that one
3 area where there might be a particularly strong case for
4 subsidies would be for vaccines for sexually transmitted
5 diseases.

6 Obviously that doesn't necessarily prove that
7 there's scientific opportunities there. It just
8 suggests there if there are scientific opportunities,
9 the economics might inhibit investment in this.

10 Let me talk about another piece of work which is
11 joint with Chris Snyder again, but also with Heidi
12 Williams, which is thinking about epidemiologic
13 externalities, so this is an area where Philipson and
14 others have done work. What we tried to do in this is
15 think of an epidemiological model and combine it with an
16 economic model. Say under what circumstances -- we know
17 their incentives to develop vaccines or for that matter
18 drugs won't be sufficient if there are epidemiological
19 externalities, it my taking the drug or vaccine benefits
20 other people.

21 But for what types of diseases is the social
22 value going to greatly exceed the private value? So we
23 set up a combined epidemiological and economic model,
24 solved the consumer problem, when will they buy it; then
25 solved the firm problem, given the consumer behavior,

1 what's the firm's optimal pricing and then derive some
2 results about how social and private incentives compare.

3 So think about a non fatal -- this can be in
4 some ways a very simplified model, even more simplified
5 than the other one, we'll think about a non fatal
6 disease, herpes, for example. Assume there's a constant
7 population, birth rate and death rate, so the population
8 stays constant. This is a standard epidemiological
9 model. Total consumer population will normalize to one.

10 So V is the fraction of consumers who are
11 vaccinated at time T . I is the fraction of consumers
12 who are infected. S is the fraction of susceptible
13 consumers, and all those things sum to one, so everybody
14 is in one of these three classes. Q or quantity is the
15 fraction of newborns vaccinated.

16 So for now, I'm just going to be purely
17 epidemiological, I'll take that as given, and then later
18 solve for the equilibrium number of vaccinations given
19 the economical half of the model.

20 So what's the rate of the change of the
21 vaccinated population? Well, the addition to the
22 vaccinated population is the people who get vaccinated
23 in each period, and the subtraction is the number of
24 vaccinated people who die. They die at the rate of
25 γ like everyone else. This is a non fatal disease.

1 What's the rate of change of the infected population?

2 Well, it's the number of newly affected people, which is
3 the number of susceptible people times the beta, which
4 is an infection parameter times the number of infected
5 people because an infected people -- people get infected
6 when a susceptible meets an infected.

7 And then the reduction in the number of infected
8 people is the number of infected people who die, which
9 is they die at the rate of gamma. The susceptible
10 population is just everyone else.

11 So then to solve for the steady state of this
12 model, just set all these things equal to zero, so I'll
13 just drop the T argument for steady state values, and it
14 turns out that the steady state number of vaccinated
15 people is just the rate at which people get vaccinated
16 divided by the death rate, this is a Pison model. The
17 number of infected people is one minus the number of
18 vaccinated people minus the number of susceptible
19 people.

20 The number of susceptible people is the birth
21 and death rate divided by the infection rate, so if you
22 have a very high death rate, then that's going to tend
23 to make it difficult for disease to spread. People die
24 before they pass the disease on. A high infection rate
25 will increase the number of infected people.

1 So for a disease to survive, the infection rate
2 has to be faster than the death rate. That's a standard
3 epidemiological result. So define the death rate over
4 the infection rate as a measure of how rare the disease
5 will be in steady state in the absence of a vaccine.

6 What's the firm problem? Well, the firm has to
7 choose a vaccine price, and we'll assume it's set by a
8 profit maximizing firm. We'll just focus on steady
9 states. We'll just assume they're maximizing steady
10 state profit. That will keep the algebra simpler.

11 So we'll consider a case for this no fixed cost
12 but there's some cost of administering the vaccine.
13 These are more complicated versions, but the algebra
14 gets more complicated, so the firms -- the flow revenue
15 for this is the price that they're charging minus the
16 cost times the number of people who are taking it. The
17 number of people taking it is going to depend on the
18 price, as well as on the epidemiology.

19 Let me speed up a little bit. So the vaccine
20 demand, consumers are going to weigh the price of the
21 vaccine on the one hand versus the chance of infection
22 on the other hand, and we'll assume that the rate of
23 harm suffered by people from having the disease is H , so
24 then you think, well, what's the harm of having this
25 disease? Well, it's H , the period of harm, time their

1 future life span which is one over gamma.

2 A consumer thinking about whether to take the
3 vaccine thinks about the chance that they're going to be
4 infected over time times the harm if they are infected,
5 and that's given by this expression.

6 So if there's a given price, then at a
7 particular price, the equilibrium demand is going to be
8 at the intersection or steady state equilibrium demand
9 is going to be the intersection of these two curves.
10 One is the correspondence between the number of people
11 -- the epidemiological correspondence between the number
12 of people taking the vaccine and the steady state
13 infection levels, so the more people take --
14 epidemiologically, the more people take the vaccine, the
15 lower prevalence.

16 On the other hand, people's demand for the
17 vaccine, while at a given price, if the prevalence of
18 the disease is below a certain level, nobody is going to
19 demand the vaccine because it won't be worth paying for.
20 If price is above a certain level, then everyone is
21 going to demand the vaccine. Remember, this is very
22 simple here. Everyone's identical here. There's no
23 heterogeneity I'm willing to pay, so there's a given
24 level price at which people are indifferent whether or
25 not to take that.

1 The equilibrium demand will be given by the
2 intersection of those two curves, so the firm's problem
3 then is to say, Well, we can think about what price we
4 want to charge, depending on if we charge a lower price,
5 then we'll have a different crossing of those two
6 curves. If you charge a higher price, you'll have
7 another crossing. What's the optimal price for us?

8 So when you solve that, you can compute the
9 steady state flow of profits for any price, find the
10 first order condition for profit maximization, and it
11 turns out you get a profit maximizing price.

12 Let me skip through this and get to sort of the
13 meat of this, so you can get analytic expressions for
14 the price, for the quantity, for profits, for welfare.

15 It turns out, and I'll give some intuition for
16 this in a minute, but it turns out that the externality
17 per dose is going to be here, that's the harm from the
18 disease, times the square root of this expression I gave
19 before, which was this expression is just a measure of
20 how rare the disease is.

21 So for every person who gets immunized, the
22 positive externality they cause for other people is
23 going to be in the square root of this expression, which
24 is the rarity of the disease without vaccination, so
25 what's the intuition for this?

1 Well, imagine you have a disease which is very,
2 very prevalent. If you have a disease which is very,
3 very prevalent, if I take a vaccine, I am mainly
4 protecting myself. I'm not going to do that much good
5 for anybody else because suppose we get exposed to this
6 vaccine a thousand times a year or exposed to the
7 disease a thousand times a year. So then I protect
8 myself, and so somebody else gets exposed only 999
9 times. It doesn't make that much difference to them.
10 The benefit of the vaccine is primarily for the person
11 who takes it, and therefore the manufacturer is able to
12 charge pretty much -- if they charge the private label.

13 Now, take the other extreme, think about a
14 disease that's just on the edge of being eradicated, and
15 this is a disease where the net -- what's called the net
16 reproductive rate, for each primary infection, is just
17 above one so that means when someone is infected, they
18 pass it on to just slightly more than one person before
19 they die in a population where nobody has yet been
20 exposed.

21 In that case, it's a very rare disease.
22 Somebody who vaccinates themselves is protecting
23 themselves against something that probably is not going
24 to hit them, but if it does hit them, then there's a
25 huge social benefit because they're just on the edge of

1 being able to -- just on the edge of being able to
2 eradicate this disease by vaccinating a few people, and
3 in this model, you never actually get to eradication as
4 Tom has shown and similar to Tom's work.

5 But in the limit, as this disease goes to the
6 level at which it would just barely survive in the
7 absence of a vaccine, the entire benefit of vaccination
8 is a social benefit rather than a private benefit, so
9 what this is suggesting is that, and in fact in this --
10 at least in the simple example, the benefit approaches
11 the benefit of preventing a case of the -- the social
12 benefit that doesn't accrue to the individual approaches
13 the benefit of a single case of infection with
14 certainty.

15 So what this is saying is if you think about
16 various diseases, compare a very common disease that
17 maybe doesn't cause that much harm like the common cold.
18 In that case, the market is going to do reasonably well.
19 The private benefit and the social benefit might be
20 reasonably close to each other. Now think about a
21 really rare disease but with lots of intense harm.
22 That's the one where there's going to be a huge
23 discrepancy between social benefit and private benefit.

24 So what are the conclusion of this? Well,
25 first, for sexually transmitted infections, the ratio of

1 social to private value might be greater for vaccines
2 than for drugs, so we might want to think about policies
3 that increase the private incentive to develop those,
4 and that could be -- of course at this point that's
5 silent on the question of, do you do that through push,
6 through more funding variety, or do you do that through
7 pull by making the commitment to help subsidize the
8 purchases of a vaccine if it's developed? There might
9 be other considerations that would pay for one or the
10 other. One would be, if you don't know what the science
11 is, you don't know what the feasibility is. Then if you
12 go with pull, you know you're not wasting your money.

13 Another approach, another result is for
14 infectious diseases, the ratio of social to private
15 value will be largest for rare diseases, so this would
16 provide one more justification for something like the
17 Orphan Drug Act, and obviously there are many pluses and
18 minuses for the Orphan Drug Act, and the Orphan Drug Act
19 doesn't just apply to infectious diseases, but it does
20 provide a rationale at least in that case.

21 Given that the value , a lot of the results that
22 we got were not on the total difference between social
23 and private value. They're on the ratio of social to
24 private value or on the social value per immunization,
25 so they provide pretty clear guidance for how much of a

1 subsidy you would want to pay if you were doing a pull
2 program where you're paying something extra to the firm
3 for every person immunized.

4 They might -- for the amount that you pay for
5 push, that would be obviously non monotonic in the
6 incidence of the disease. If it's a very common
7 disease, people would be willing to pay almost the full
8 private value. If it's a very rare disease, or the
9 ratio of social to private value is very high, but if
10 it's a rare enough disease m that aren't that many
11 people who get it, so the total social value isn't that
12 big.

13 So I think this does have -- these basic points
14 will apply independent of whether you go with push or
15 pull financing or what combination you choose, and
16 clearly it's not either or. It's a combination that
17 you would want, but they do have some -- they might
18 provide guidance as to how you would structure a pull
19 program as well.

20 Thanks very much.

21 (Applause.)

22 MR. ADAMS: Why don't we have some questions, if
23 you would like.

24 DR. RYAN: Yes. I'm Una Ryan. Very nice talk.
25 I just wanted to take you to task a bit on the issue of

1 the vaccine protects only the individual.

2 The model I think needs to take into effect the
3 herd effect where if almost all of the people in a herd
4 or a village or whatever are immunized and protected, it
5 protects those who aren't, and that's what we're losing
6 in this country. As people drop out of immunizations,
7 we're losing the herd effect, and they are able to
8 infect others, but it's a very well known concept in
9 infectious disease studies, and I think it actually
10 probably argues more strongly for some of the things
11 that you're saying.

12 MR. KREMER: Oh, yeah. This definitely -- I
13 mean, the motivation behind this work with Heidi and
14 Chris is exactly this herd immunity, so we're trying to
15 get at the question of when is the herd -- it's always
16 going to be there, so there's always some positive
17 benefit to other people, and even in the case of a very
18 common disease, there's some benefit to other people of
19 taking it, so I'm probably speaking too loosely if I
20 implied it wasn't there at all.

21 We're trying to find what's the ratio of the
22 private benefit to the social benefit, and for the rare
23 disease, that ratio can acidotically approach infinity.
24 It's almost entirely social benefit. For common
25 diseases, the greater proportion of the overall benefit

1 is private, but we're definitely exactly about that sort
2 of herd immunity in epidemiology.

3 MR. MILLER: Dean Miller. Why can't we just use
4 life insurance to solve this problem when you've got
5 you have rare incidence of a disease and it's
6 essentially an exogenous event about you being infected?
7 We fully capitalize that into an insurance policy and
8 then not worry about the development of a vaccine.

9 MR. KREMER: So I guess I would have two replies
10 to that. The first one is if in a developing country
11 context, in which I often work, there's very little life
12 insurance but even in a rich country context like the
13 United States, if there are many different life
14 insurance companies out there, it's not clear that any
15 one of them will have sufficient incentives.

16 So this is exactly as Una was pointing out, this
17 is a herd immunity issue, so then there's an externality
18 across the different life insurance companies. If one
19 life insurance company is helping finance purchase of a
20 vaccine for people, then they are going to be conveying
21 a benefit to all the other life insurance companies.

22 So even life insurance companies won't fully
23 internalize this unless there's a single effectively a
24 national health system or something like that.

25 MR. MILLER: You misunderstand. I mean to not

1 develop the vaccine at all, for a sufficiently rare
2 disease, just allow life insurance to fully internalize
3 the risk.

4 MR. KREMER: Right, so in a richer version of
5 this model, I wrote down a very simple version where
6 there's no cost to developing the vaccine or drug, which
7 is obviously very artificial. In a richer version of
8 this model, there's -- for the appropriate parameter
9 values, it just is not appropriate to develop -- it's
10 not appropriate for society to develop this, and even if
11 there was no life insurance, unfortunately there's lots
12 of things that we can't do as a society.

13 And so this would -- one of the things that this
14 provides guidance to is when is the private incentive
15 going to match the social incentive to invest in the
16 R&D? And in general, in both these models, the private
17 incentive to invest will be less than the social
18 incentive, so even if it's worth it for society, it may
19 not be worth it for a private firm, if they're
20 relying -- even if there is insurance companies.

21 But if you spread the parameter values, it's not
22 worth it for society either.

23 UNIDENTIFIED SPEAKER: I'm thinking about the
24 profitability of the drugs versus the vaccine, so if you
25 think about the developed country case, how do you think

1 if affects things when you account for the fact that
2 most of these drugs, let's say for AIDS, are purchased
3 by governments and people don't typically -- so if you
4 look in the U.S., between Medicaid, AIDS drug assistance
5 programs, the VA, et cetera, more than 60 percent of
6 those drugs are procured through those programs.

7 And I guess I wonder what's your sense -- the
8 thinking about the present value of expenditures through
9 those programs, the extension of life expectancy, do you
10 think -- if you compare that with what would be
11 plausible reimbursement rates for a vaccine, so have you
12 thought much about that?

13 MR. KREMER: Sure. So in the paper with Chris,
14 the model is just purely private purchase, and you're
15 right, that's not what actually happens for many of
16 these cases. Governments are doing a lot of the
17 purchasing, so in the paper with Chris, what we do is we
18 say -- we model the process of bargaining for vaccines
19 in particular, governments are often basically a
20 monopolistic buyers, so we model the process of
21 bargaining between the government acting as a purchaser
22 and the producer taking, and this is an important
23 assumption -- taking this as what -- one doing the
24 national bargaining there, we have to say, Well, what
25 happens if they don't reach agreement.

1 And our assumption is that if they don't reach
2 agreement, there are sales on the private market, so the
3 government is bargaining and pharmaceutical company is
4 bargaining knowing that's what happens if they don't
5 reach agreement.

6 Then you get a lot of these result basically go
7 through because the price that the pharmaceutical firm
8 is going to be or biotech firm is going to get for the
9 product depends on what they're going to be able to get
10 to the government, but what they get from the government
11 depend in part on what would happen if they don't reach
12 an agreement with the government and have to sell in the
13 private market.

14 MR. VANNESS: If you look at the vaccine price
15 that the government pays versus the drug prices that
16 comes out of your work with Chris, suppose that we
17 think right now life expectancy is ten years,
18 expenditures are ten thousand dollars a year, that's a
19 hundred thousand dollars, so if that's like the
20 benchmark of the drug present value, can you give us a
21 sense of kind of the model? Is it 10 or 200?

22 MR. KREMER: I see, so we haven't done that
23 calculation. Maybe we should. What we've done is in
24 the somewhat more abstract model, how does the amount
25 paid -- does there remain a distortion between drugs and

1 vaccines if the government is doing the purchasing, and
2 at least in the set up that we use, it does, but you're
3 right, while we've some calibration exercises for the
4 purely private market, we probably need to do more.
5 We've done some. I unfortunately don't remember offhand
6 what the numbers were.

7 MR. CALFEE: Jack Calfee, AEI. I may have
8 missed this in your talk, but if you're creating a
9 market rather than paying a price, an obvious problem is
10 once you've created the market, developing companies
11 will buy from unauthorized generics. How do you deal
12 with that?

13 MR. KREMER: Oh, so if you look at this -- the
14 basic approach is that the sponsors during the period
15 when -- there are two periods, the initial period and
16 then the period after the commitment is exhausted, so in
17 this initial period, you might of the developing
18 countries paying a dollar per person, but maybe that's
19 not the right number, maybe it should be \$3, whatever,
20 and the sponsor is paying \$14 per person immunized, who
21 knows whether that's the right number, but if you have
22 that price that the developing countries pay low enough,
23 and I think when you design it, you need to think about
24 this and set it low enough, so it's just not attractive
25 to buy the rip off generic that's violating the

1 copyrights.

2 MR. CALFEE: It's a commitment to match whatever
3 the developing countries spend with a larger amount --

4 MR. KREMER: Exactly, exactly. So that's how
5 you create incentive for them to not just turn to
6 counterfeits.

7 MR. PHILIPSON: Tom Philipson, University of
8 Chicago. You and I have discussed some work that I've
9 done before basically which seems to be this problem
10 where you're providing R&D incentives when there's
11 external of consumption, meaning the rare disease or the
12 neglected disease problem where the rich countries care
13 about the consumption and the poor country, whether for
14 selfish reasons or for altruistic ones.

15 So in that case it seems to be that the people
16 really benefit in an economic sense from solving third
17 world diseases or the rich countries in an economic
18 sense. Obviously they're healthier down there, but
19 they're not willing to pay enough in order for this to
20 happen, and the people willing to pay for this to happen
21 are altruistic or selfish rich countries that want to
22 take care of these countries.

23 So then I'm really confused with your and
24 Ernie's studies and also Zach's kind of arguments which
25 is: Is this cost effective? How do you measure cost

1 effectiveness when the payor is really the rich
2 countries? It's got to be valued enough for rich
3 countries because if it's cost effective down there,
4 what's the problem?

5 We just develop it and then go sell it, so are
6 people willing to pay above price down in those
7 countries, why isn't it developed? So it's got to be
8 somehow that this is altruistic effective meaning that
9 the rich countries are willing to pay for this to happen
10 beyond the price of developing it in some sense.

11 So I don't understand these -- when people
12 justify these interventions on cost effectiveness basis,
13 I don't understand that argument at all.

14 MR. KREMER: Well, let me first answer on the
15 terms of your question, and then maybe slightly
16 challenge the terms that you've said. So suppose we
17 say, Look, for whatever reason people in India or Africa
18 aren't willing to pay for this, let's justify it as cost
19 effective on an altruistic basis or selfish basis for
20 the rich countries.

21 Well, rich countries now, including U.S., are
22 paying for AIDS treatment. AIDS treatment, there are
23 numbers all over the place, but let's say that once you
24 include the cost of delivering the medical care as well
25 as the cost of the drugs, it cost \$500 per person per

1 year, so then you're paying -- let's assume then that
2 translates into \$500 per year of life extended.

3 So when Ernie did these calculations as to
4 what's the cost per year of life with the vaccines, with
5 the vaccine commitment, we get numbers like \$15.

6 MR. PHILIPSON: You're saying the altruistic
7 U.S, you're measuring (inaudible). Then you're pricing
8 that out, but the pricing out could be zero. I don't
9 care about those prices at zero, and if I care a lot
10 it's ten times the value we measure in regular studies
11 so I don't really know.

12 MR. KREMER: So what we've observed in terms of
13 revealed preference is people in the U.S. through
14 foreign and other programs and people through Global
15 Fund and us are willing to pay \$500 to save a year of
16 life with AIDS drugs with antiretrovirals, so this would
17 cost \$15 per year of life. Now, look maybe they value
18 existing lives different than life saved with the
19 vaccine, but it does at least I think create some prima
20 facie case.

21 Let me just also slightly challenge the argument
22 that while people there aren't willing to pay or else
23 that would be profitable on its own and you wouldn't
24 need a program like this. I think it's -- while it's
25 true that -- I think that would be true for some

1 products, but given the issues of intellectual property
2 and the fact there's a monopolistic buyer here, I don't
3 think that's necessarily the case.

4 Developing a vaccine requires a huge, upfront
5 investment, a very risky and large upfront investment,
6 and then you develop something where the marginal costs
7 might not be trivial, but the marginal costs are only a
8 fraction of the overall costs of development this.

9 At that point if you're a developing country
10 government, certainly if you're a small part of the
11 world, if you're the government of Uganda or even if
12 you're the government of Nigeria, why not try and get
13 the best price you can, and if you can buy something
14 that's a generic version, of course you will, or for
15 vaccines, it's not exactly generics that are the issue,
16 but in any case if you can buy a new version that's
17 cheaper, even if you're not going to be creating the R&D
18 incentives, well then, bygones are bygones, and anyway,
19 you're a small part of the overall market.

20 So I think there are important market failures
21 here in the absence of a strong international
22 intellectual property rights regime, which we don't have
23 in this sector. There are big market failures that mean
24 that even if something were profitable purely from the
25 standpoint of the developing countries, it's not clear

1 that a manufacturer would be able to capture all that
2 surplus.

3 MR. ADAMS: Why don't we have one more question
4 if there is one. You've had a chance. Ginger?

5 MS. JIN: My name is Ginger Jin from University
6 of Maryland. I have a question about your proposal of
7 pre-committal payment for vaccine, future vaccines
8 innovations.

9 Have you thought about how this proposal would
10 effect those firms' incentives in terms of their risk
11 portfolio? Is it possible that the firms now start to
12 develop sort of probably safer but less effective drugs
13 or more of me-too drugs so that they can capture this
14 market but not necessarily the best R&D we would like
15 them to have?

16 MR. KREMER: Sure. Well, this very complicated
17 and very interesting issue of how do you balance the
18 incentives for the first developer versus the incentives
19 for later superior products? And I think there's --
20 depending on how you design the commitment, you could
21 design it one extreme or another or somewhere in
22 between. That's really a choice, depending on what
23 people think is most important, and so there's some
24 flexibility.

25 I mean, you could write it to say winner take it

1 all for the first, or you could write it the opposite
2 extreme. The compromise, and I think whoever implements
3 this will have to make that decision for themselves, but
4 what the Center for Global Development working group
5 came to, and this had public health people on it, people
6 from bio, the industry organization, spent a lot of time
7 talking to firms, had lawyers on it, economists, public
8 health people. What we came to was the idea that there
9 should be -- that if a new superior product is
10 developed, it should be eligible as well, and then
11 countries could decide which vaccine they wanted.

12 If a product is just a pure me-too, and it's not
13 superior in any way, then it shouldn't be eligible, and
14 it wouldn't be on the list of products that countries
15 could choose among.

16 I think that -- I don't want to claim that
17 that's theoretically perfect. Theoretically you would
18 want to pay for the exact amount of improvement, but
19 it's hard to write a contract to do that, but I think it
20 roughly kept would create the right incentives. It
21 creates incentives to some people to try to produce
22 something quickly, and it creates incentives for others
23 not to produce pure me-toos, which would weaken the
24 incentive for the first developer, but to work on
25 something if they think it's going to have a realistic

1 chance of being superior.

2 That's a rough compromise, and certainly you
3 could argue about we should adjust the margins
4 somewhere.

5 MR. ADAMS: I would like to thank Michael for
6 rushing over here from the Gates Foundation to give a
7 talk, and also for your work on this area. It's
8 obviously of huge importance, and I'm grateful for how
9 much work and effort you've put into it, so if we could
10 give Michael a round of applause.

11 (Applause.)

12 MR. ADAMS: So we'll have about 20 minutes so
13 you can rest, chat amongst yourselves, and then we'll
14 come back here.

15 (A brief recess was taken.)

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1 PRESENTATIONS: PHARMACEUTICAL R&D AND BIOTECH
2 DEVELOPMENT

3 CHAIR: LAURA HOSKEN, FTC, BE

4 PRESENTER: ANDREW METRIC, Cornell

5 DISCUSSANT: PIERRE AZOULAY, MIT Sloan

6 PRESENTER: SCOTT STERN, Northwestern Kellogg

7 DISCUSSANT: LOREN SMITH, FTC BE

8

9 MS. HOSKEN: Good afternoon. I think we should
10 get started so we don't run behind. I'm Laura Hosken.
11 I'm an antitrust economist at the Federal Trade
12 Commission, and I will be shepherding us through the
13 next session which is all about innovation. Our first
14 paper is going to be given by Andrew Metric which is
15 going to discuss how financing -- oh, it's a title
16 change. Can a Liquid Market Save your Life? I like the
17 title. So I'll pass it off to him.

18 MR. METRIC: Thanks very much. Thanks for
19 letting me substitute pitch for Sean here today. Sean
20 is up in Boston presents his more sexy paper than this
21 on autism and television.

22 I wanted to just start talking, I'm a financial
23 economist so this is an unusual opportunity for me to
24 speak to a group that has more knowledge of health
25 economics, and it's a great topic. It's been a lot of

1 fun working on this, and I'm inspired a bit by the
2 example that of Michael Kremer. Michael was a graduate
3 student classmate of mine. We started the same year in
4 Harvard. We were in the same study group, and I can
5 tell you he had just returned four years in Africa, his
6 first bout with malaria. How many have there been?

7 MR. KREMER: Two.

8 MR. METRIC: Just two, and he didn't know
9 anything about economics, just absolutely nothing. He
10 was completely ignorant and we thought we would have to
11 carry this guy through graduate school. Within months,
12 it is was clear he was an unusually creative economist,
13 and he's made us all very proud. I can say as an
14 outsider to this literature that it is -- it's a
15 literature that makes me proud to be an economist. I've
16 made no contribution to it, but it's clearly very
17 important stuff, so to everybody that works on it
18 including Michael, thank you.

19 Now, for this one. This title I should
20 apologize for a little bit. I know that health
21 economists, Sean doesn't like this title. Sean likes
22 the title that you have on your sheet, and I know that
23 Pierre has already told you he doesn't like the title.
24 Health economists don't like this tile because they take
25 this thing about life saving very seriously. If you

1 want to say you have saved lives, you have to prove you
2 saved lives.

3 This is different is for me. This is a tongue
4 in cheek title aimed at the finance world. In the
5 finance world we have huge debates about whether, not
6 going to use this stuff I'm too loud without it, so if I
7 we have huge debates about whether or not asset markets
8 matter for anything real, so you have the stock market.
9 You have the bottom market. They're jumping up and down
10 all the time. Is this a side show to an actual economic
11 activity or is this real?

12 And most of the work that's been done on this
13 looks at measures of market activity and then tries to
14 find some indication that it has affected some form of
15 investment activity, mergers and acquisition activity,
16 capital expenditure, et cetera, but these are course
17 measures.

18 What you really want to do, what the Holy Grail
19 is in corporate finance is to get down to the project
20 level. Can we identify individual projects within firms
21 and see whether or not what's going on in stock markets
22 affects those projects? So that's the motivation for
23 this, which is that it turns out that pharmaceuticals --
24 it was like it was an industry created by God just so we
25 can study things like that. They have new projects that

1 have been careful with the gates. You have to go
2 through the gates knowing you've moved from phase 1, to
3 phase 2 to phase 3.

4 We don't have perfect data, but we have much
5 better data than we have for anything else. Compare
6 this to figuring out what IBM is doing in R&D projects.
7 It's totally hopeless, and we have it for the whole
8 industry going back for many, many years, so the main
9 idea is let's look at what's going on in new markets and
10 see if the liquidity cycles in asset markets are a
11 driver of what's happening at the individual investment
12 level.

13 So that's the game, and health economists who
14 are annoyed by this or are absolutely fair to
15 be annoyed, I'm not going to say anything about life
16 saving, we're going to say something about drug
17 development, as a non health economist, I sort of feel
18 like more drugs is good, but I know that's a big debate
19 in your world, but we're going to be talking about more
20 drugs, okay, so here we go, legal drugs that is, what do
21 you guys call them, patent drugs or ethical drugs, that
22 the word.

23 So here's the story. The first is as we all
24 know, biopharma firms spend an enormous amount of R&D.
25 The next closest industry is spending half of that, and

1 we think that new technologies are the drivers here, and
2 what we would think is that capital markets were working
3 perfectly. We didn't have any problems in capital
4 markets, and every positive NPV project would always get
5 financed, and no negative NPV projects would get
6 financed, and we would not see any effect of financial
7 markets by themselves. If we had something exogenous in
8 financial markets, we wouldn't see any effect on drug
9 development, so that's what we're actually going to
10 test.

11 So here we go. This is a very complicated
12 economics, the kind of stuff Kremer could not do when he
13 first showed up at Harvard, which is a nice supply and
14 case. He knows that's true. Now he's a little bit
15 better, but at the time nothing. So what do we have
16 here? Demand and supply, and if this is the supply of
17 capital, right, if we really have these perfect,
18 efficient markets that are always working really,
19 really, then all right, we have some perfect capital and
20 this is what you do, but if instead you have an
21 upward sloping supply curve as you have anywhere else in
22 the world, and in fact it's not so easy to raise so much
23 capital that you want, then you can be constrained and
24 you might not be able to do all your positive NPV
25 projects.

1 So if you then get a nice good shock and you get
2 deeper capital markets, suddenly you can do some more
3 projects so this is our motivation, and the first
4 prediction that we started with -- prediction is a funny
5 word when you don't have a model, but the first
6 intuition that we started with is, Okay, when up have
7 tight financial conditions, people are going to pull
8 back on the investments that they do, so we're going to
9 see fewer investments, fewer drugs started, but the ones
10 that are started are going to be better in some sense.
11 They're going to have a higher probability of going on
12 to the next phase, for example.

13 So that was our initial prediction, but then
14 there are other things that one has to think about. The
15 most important one I think here has to do with
16 adjustments on the intensive versus the expensive margin
17 stores, so if there's a lot of money out there, one
18 thing that you might do is you might actually do better
19 in trials. You might put more people into the trials,
20 spend more money on each trial which might increase the
21 chances of it moving on to the next stage.

22 Okay. So here's just the types of stylized
23 facts people are already aware of. In 2000 we have all
24 the press about the humans geno product being completed.
25 Everyone thinks this is going to revolutionize medicine

1 so biopharma firms area able to raise enormous amount of
2 capital, \$32 billion in that year, a lot higher than the
3 other years, and what does that do?

4 That's going to be wonderful for their balance
5 sheets, so here you can see just sort of a standard.
6 This is how many years do you have at your current cash
7 burn rate before you run out of cash, and you can see
8 that 25 percent of them had greater than five years, and
9 as of 2000 after that big year, 42 percent of them did.

10 So you can take all that money, they can --
11 well, what I -- the way I view these firms of course
12 knowing no science at all, I just think of them as black
13 boxes. You put in money, and out comes drugs, so this
14 is the game. There's a lot of stuff that goes out in
15 the middle, but that's the basic game, so if we put in
16 money, more drugs should come out, how would this work.
17 I don't have to give you guys that slide that we ripped
18 off from probably someone in this room about the drug
19 development process.

20 Here's our data, and it's data that a lot of
21 people probably have already worked with, pharma
22 projects data. We're going to supplement pharma
23 projects data with data from NDA, the people who bring
24 you the pink sheets because people who have worked with
25 pharma projects data probably know, they're going to

1 give us a snapshot in time of all the drugs in
2 development.

3 It will tell us when those drugs went to each
4 stage, but it will list under Pfizer all of Warner
5 Lambert stocks, and if we want to know that it was
6 Warner Lambert that really did it, we have to find
7 something to enable us to go back in time, so NAD has
8 hard copy books, so we just combine those two things.

9 That was the hardest part of the project. We
10 have even lost the coauthor because it's taking so long,
11 ran out of patience, but eventually we did it by
12 outsourcing a lot of it to Cambodia, believe it or not,
13 where our books got coded into computer files, and we
14 were able to match them, and now what we're going to do
15 is take the information from Pharma Projects data.

16 We know the date the drug begins each
17 development or Pharma Projects does their best to try to
18 estimate such a date, talking about it because the date
19 in the file is just not the date that they got the
20 information. It's their best guess of when the drug
21 actually entered that phase, and then we have an
22 aggregate liquidity index which I will show a minute and
23 explain what it means, and then we have measure of burn
24 specific financial constraints, so we have time series
25 variation on the aggregate level for what's going on in

1 markets, and then we're going to have cross-sectional
2 and time series variation at the firm level of how
3 financially constrained those firms are.

4 And here we're just picking stuff out of the
5 finance literature so there's no invention here. These
6 are all famous themes in the finance world, so just to
7 get a sense of the data, again I don't think -- this is
8 not going to be unfamiliar to people in this room. I
9 know we have people that work at the FDA, maybe they
10 have this implanted in their brains. They know what
11 this looks like. For me it was revelatory, what the
12 pictures would look like, and there is some trending.

13 So we can see that for each of these phases
14 compared to the beginning of our sample period, '89-90,
15 there are somewhat more drugs going into each of the
16 phases of development throughout our sample period.

17 Down at the bottom are new preclinical trials.
18 They're down at the bottom, and I should say by the way
19 this day is not perfect, so you see things that show up
20 in the data set under pre clinicals and then don't show
21 him again until phase III. That does happen. You will
22 also see drugs that you will never see -- oh, sorry.
23 That was bound to happen, right. Let me keep walking
24 over it.

25 And you will also see things that will first

1 show up in phase II. Now clearly that's not because the
2 FDA is letting them first show up in phase IIs. It's
3 because Pharma Projects never found out when it went
4 into phase I or phase II trials. So it's not a perfect
5 data set. We would like to get a perfect data set. We
6 begged the FDA when we started the project, and they
7 were extremely nice in telling us no in lots of
8 different ways, so this is real the only way that we're
9 able to do it.

10 So here is an aggregate liquidity. Just think
11 of this as a measure of how deep capital markets are at
12 any point in time. The way that it's actually measured
13 is extremely long and involved and has nothing to do
14 with issuing behavior, so specifically we don't want a
15 state variable here which is like the amount of money
16 that biotechnology is raising in the capital markets.

17 That kind of state variable would have a problem
18 because it wouldn't just be about liquidity. It also
19 would represent people's belief about the quality of
20 drugs in the pipeline. We want to get far away from
21 that. We want to have a state variable which has
22 nothing to do with people raising money say in biotech,
23 but just a generic variable about the liquidity of
24 markets.

25 So the exact way that this is built as I say

1 isn't crucial, but the basic idea is the authors,
2 Pasture and Stanbaugh in the paper in 2003 looked on a
3 company by company basis at how much companies kind of
4 bounced back on a second day after having a big fall on
5 one day or drop on a second day after having a big rise.
6 How much do they have to move into the depth of the
7 market? And so they had to take a price hit because
8 they moved into the depth of the market, and then they
9 just aggregate that.

10 So just think of it as a state variable, of
11 which there is many others. It's not like this is the
12 only state variable, but this is a nice one because we
13 know it's pretty pure and not being contaminated by
14 biotech firms raising money, so it us a state variable
15 of how liquid the market is.

16 You can see that the negative places on here,
17 they do conform to intuition '87, when we had a stock
18 market crash, and then we have one down here, '97-98,
19 this is the Russian debt crisis, LTCM, and then one down
20 here when the market starts falling, and then kind of
21 following September 11, so you can get things that look
22 somewhat sensible, but as I said, this isn't our
23 measure. This is a measure that's out there in the
24 finance world.

25 So here are the results very quickly. How am I

1 doing? I have five minutes now? Oh boy, I'm going to
2 talk very fast.

3 So does aggregate liquidity affect the quantity
4 of drug developed? So this is a regression, put number
5 of drugs on the left-hand side, and then that index on
6 the right-hand side, total for the whole industry so
7 it's not a firm by firm regression, so we're going to
8 pool everything, all different phases which will then be
9 dominated by preclinical, and then we'll also get a look
10 at each phase separately and everything is measures as a
11 ratio to 1999, that's our numerary here, and basically
12 you see that wherever you have stars, which means
13 significance, you have positive numbers.

14 So the more liquidity there is, the more drugs
15 we're getting developed, overall aggregate in the whole
16 industry. Here's the F test on joint significance.
17 It's significant for everything except phase I, which is
18 pretty cheap compared to the stuff that comes later, so
19 we think, Well, that one doesn't matter as much.

20 Okay. Question 2: How about firm specific
21 financial constraints? So now we're going to run a firm
22 level regression, and the dependent variable is going to
23 be the number of drugs originated by company J that
24 interface K in the year T. So for each phase, you can
25 run a regression of the number of drugs in that phase,

1 and it's a negative binomial with firm fixed effects,
2 which the only thing that means is the way you interpret
3 variables, is if a parameter, coefficient is less than
4 one, that means that there's less of it happening, and
5 if the parameter is more than one, it's more of it
6 happening, so I'll just skip this data slide.

7 So the basic thing there, this is a measure K Z,
8 this is called a Kaplans and Golex Index (phonetic).
9 This is a firm level measure of whether the firm is
10 financially constrained. The higher this measure, the
11 more constrained is the firm. We've put it in
12 percentile terms, so it's just the quintile of their
13 constraint method. The actual number is meaningless.

14 So preclinical, you can see that the more
15 constrained you are here on the preclinical side,
16 looking at the joint significance of the firm level
17 variables, they only matter for preclinical. For
18 everything else we're following that the firm level
19 stuff doesn't matter.

20 Now, all we're capturing here is time series
21 variation. Most of the action is probably in the
22 cross-section, but we have firm fixed effects, which is
23 taking this out, but the time series variation in a
24 firm's financial constraints is falling -- it matters
25 just for preclinical.

1 For the aggregate liquidity measures, everything
2 is significant at least 10 percent level, 10 percent
3 being the new 5 percent in economics, right, because we
4 like thinks to being significant. Everything is showing
5 up significant except for phase I, and it's very strong
6 here and in preclinical and in phase III, which is
7 somewhat surprising, so you get a lot more liquidity.
8 People are more likely to move something along to phase
9 III.

10 Now, the question then becomes, I'm going to
11 skip that and go right to question 3, how about quality
12 of drugs? Are they really just doing this on the
13 margin, taking a marginal drug and putting it in, which
14 is what we expected and which would be a simpler story
15 to tell, but it is not the story that the data want to
16 tell.

17 So we do find that maybe there's not -- I don't
18 think we have a data slide on this, so I'm just going to
19 have to describe it. Here's the summary of the results.
20 A one standard deviation decrease in the financial
21 constraints two years ago gives lower survival
22 probabilities for projects initiated in year T.

23 So what decrease means in the K Z measure is
24 you're less constrained, so if you were less constrained
25 in the past, then idea you're less constrained -- you

1 put more marginal things in, and they were less likely
2 to go on. That's what one would expect, but that's not
3 what we find when we look at it for aggregate liquidity.
4 For aggregate liquidity, we find quite strong results
5 that if you have more money out there in the whole
6 world, the whole stock market is more liquid, not only
7 are we getting more projects but they are better, better
8 in the sense of having a higher probability of moving on
9 to the next phase.

10 There's a lot of data things that I don't have
11 time to talk about or would be boring even if I did have
12 time, but we try tried as hard as we could to be careful
13 about whether these were being given by -- I don't
14 really want this result, it's harder to explain but it
15 does seem to be robust and true, and that won't go away
16 when we do lots of other things.

17 Let me jump right to the conclusions so I have
18 one minute? One minute.

19 So financing has a real effect on both the
20 quantity and quality of drugs developed. That's what
21 Sean would like the title to be, zzzzz, it's really
22 boring, but okay. When capital is relatively plentiful,
23 firms develop more drugs, and those drugs are more
24 likely to advance.

25 Firms facing new financial constraints develop

1 more preclinicals. It's only really in the preclinicals
2 that we see it, and the preclinicals and phase I drugs
3 are less likely to advance, which is what we would
4 expect so that's more along the lines of they are
5 holding back on the drugs that are the marginal
6 projects.

7 The aggregate liquidity has a stronger effect
8 and may be swamping some of the firm specific stuff, and
9 that's just because the firm specific stuff, we're just
10 capturing the time series variation.

11 We do not have any good way to estimate whether
12 the projects that are going forward are these high
13 impact projects that are being kept off, kind of high
14 impact, low probability or me-too drugs. We don't know,
15 so we would really need to dive in deeper into that, and
16 that's why our next phase is to look at oncology.

17 So oncology as has been shown by David
18 Scharfstein and Elon Guedj, there's some very, very good
19 data you can get at the trial level for oncology, and
20 who the people were in the trials, how long the trials
21 took. We can get better data on that so we can try to
22 drill down a little bit more deeply into what is going
23 on at the investment level.

24 Okay. That is it for me. I want do the extra
25 slide.

1 (Applause.)

2 MS. HOSKEN: Pierre is going to be our
3 discussant.

4 MR. AZOULAY: It's my first time in D.C., and
5 I'm very disappointed CSPAN didn't show up

6 So it's clearly a very important agenda that
7 Andrew and Sean are taking on, and sort of trying to
8 identify the effect of capital marketing efficiencies on
9 R&D investment in a setting where we think there is
10 actually a very complicated relationship between
11 investment and health outcomes as well.

12 So this is sort of early state research. It's
13 sort of my take on the paper is that it clearly has the
14 potential to become something sort of interesting and
15 really nice, sort of external capital market companion
16 to the paper of Guedj and Scharfstein which was mostly
17 focusing on internal capital markets.

18 So my view of sort of looking at sort of
19 research papers is that you need to have a hypothesis, a
20 lever and then a result, so the hypothesis is there are
21 really affects of market liquidity and financial
22 constraints on R&D investment.

23 The lever that -- to get at this hypothesis that
24 Andrew and Sean are using are those two indices that if
25 you're not steep in the financial economics, that you

1 probably already new. They were sort of -- well, one of
2 them was totally new. The other one I had heard of
3 before. The Kaplans and Golex Index to measure a firm
4 specific financial constraints, and the Basso Stumbo
5 Index (phonetic) to measure aggregate liquidity, and so
6 in short, the result is that they find rather large
7 effects, and they're unevenly distributed against phases
8 of investment.

9 Okay. So here are the things I really like
10 about this paper. First this attempt to distinguish
11 aggregate liquidity constraints from firm specific
12 circumstances, which at least in my maybe circumscribed
13 view of the world, it is the first paper that I saw that
14 sort of achieved that, and also there is a literature on
15 sort of equity cycles in the venture capital literature,
16 and it's all about hot and cold market, and as far as I
17 can tell, the way people decided whether market was hot
18 or cold is Paul Gompers would put his finger in the air
19 and see if the wind was blowing and would decide whether
20 it was hot or cold.

21 So clearly the index that they're sort of using,
22 the Basso Stumbo Index is going to be a much sort of
23 nicer measure to sort of look at that.

24 The other evidence that is in the paper that
25 Andrew isn't talk about at all are the anecdotes from

1 biotech CEOs, and they're just anecdotes but they struck
2 me as sort of very, very interesting, and I wish they
3 could maybe try to test in a sense some of the
4 indications of those anecdotes more directly.

5 Now, the most interesting result I found in the
6 paper is also somewhat varied. It's actually not about
7 the main effect of the firm specific -- the firm
8 specific variable in sort of the market, the aggregate
9 market variable. It's the interaction. You have the
10 result, and it's only, if I remember right, from
11 preclinical, and if you take this result seriously it
12 means that managers consider financial constraints to be
13 more severe when they occur in a liquid market.

14 Now, to me that's not immediately intuitive.
15 It's both interesting and not immediately sort of
16 intuitive why that would be the case, and I think they
17 should push harder on this result and I would give it
18 much more prominence.

19 So a few issues that I have with the paper.
20 Generically given the empirical strategy that they have,
21 my sense is that it could have run very similar models
22 on a cross-section of industries, and in fact they
23 probably should do that. The Kaplans and Golex Index
24 and the Basso Stumbo Index can calculate for any
25 industry. What they're -sort of gaining on focusing on

1 the pharmaceutical industries really is sort of this
2 ability to distinguish the different phases of
3 investment.

4 But there's a sense in which I wish almost which
5 would be more idiosyncrasies of the pharmaceutical
6 industry in the paper, so can one in a sense exploit
7 small experiments that are really due to idiosyncratic
8 features of the industry in terms of actually measuring
9 financial constraint as opposed to using an index that
10 in a sense is a general purpose index, okay?

11 Now, there's a lot of emphasis in the paper
12 about sort of the fixed effect and what that you maybe
13 buy you or not buy you. My sense is that maybe I sort
14 of misunderstood what the case index is, but I kept
15 thinking about exactly what was driving changes in the
16 Kaplans and Golex Index, and if I've misunderstood,
17 maybe I misunderstood part of it are there changes are
18 being skewed, so I'm not sure this is actually -- I'm
19 not sure this is the same thing, whether fixed
20 difference is going to buy you that much. They're going
21 to take care of some problems, but it's not clear why
22 that in a sense there should be more across a cross
23 section than within firm dimension of the data.

24 Now, I think the really big deal for me when
25 trying to think of this problem is that I would imagine

1 that the effect could be very different for established
2 pharmaceutical firm who has potentially very large
3 internal capital markets versus the biotech firms that
4 are much more dependent on what's happening on the
5 public markets, and I think the authors know that
6 because all their anecdotes actually pertain to the
7 biotech segment of the industry.

8 So at the very least, I would like to know how
9 those results change, become stronger or weaker if we're
10 focusing only on biotech, and by biotechnology I don't
11 mean -- I'm not interested about the molecule or the
12 weight of the molecule. I'm basically interested about
13 whether those firms have internal capital markets. In
14 general it seems to me that looking -- they've focused a
15 lot on sort of how those effects cut across certain
16 phases, but sort of trying to differentiate them across
17 types of firms would be at least if not more
18 interesting.

19 So it's very easy for a discussant to say, you
20 know, this thing might be endogenous, and I'm worried
21 about how to enter for the coefficient^m but I want to
22 try to go sort of the extra mile and try to actually
23 suggest some avenues where one might actually look for
24 meaningful shocks to be exploited sort of look at this
25 particular issue.

1 Generically I think it might be possible to find
2 some drug classes or diseases that experience some sort
3 of shock versus others, so for example Vioxx is
4 withdrawn. That also has implications for all the other
5 firms that have Cox 2 inhibitors in the market. One
6 could actually look at shock values by other
7 researchers, and I'm thinking of the vaccine shocks that
8 Amy Finkelstein had in her paper in 2004.

9 Also the shocks that come from political
10 pressures and political economy, so for example, in 2001
11 the federal government sort of threatened to expropriate
12 Bayer's on Cipro in the wake of the Anthrax scare, and
13 one might think that that would have sort of a large
14 impact on antiobiotech drugs, and this is sort of well
15 documented and similarly for AIDS, there's sort of the
16 conference in Johannesburg in 2000 that really sort of
17 put the issue of access to an antiretroviral drugs to
18 the floor, and then once one has sort of the meaningful
19 source of exogenous variation, then one can ask how
20 aggregate liquidity would moderate investment response.

21 Okay. I have sort of quibbles and little
22 things, but I can sort of talk one-on-one with Andrew
23 and Sean on those. So thank you.

24 (Applause.)

25 MS. HOSKEN: So we have a little time. Andrew,

1 did you want to follow-up with anything or should I take
2 questions from the audience the next speaker?

3 MR. METRIC: I can follow up with Pierre one on
4 one. Thanks for your comments.

5 MS. HOSKEN: Does anyone else have a question or
6 a comment? If that's the case, then let's move on to
7 Scott Stern, who is our next paper discussant.

8 MR. STERN: I think that Andrew and I were
9 chosen for this part because it's kind of after lunch
10 and after Michael had his presentation so you needed
11 people who are loud and boisterous, so I imagine if
12 Andrew and I co-taught a venture capital class, the
13 students would be at least go deaf.

14 So I want to talk about some work with Fiona
15 Murray at MIT, and it's kind part of a broader
16 research agenda that both of us -- she and I have been
17 working on with a bunch of other people, some of whom
18 have been mentioned and kind of Ernie and the Bureau of
19 Productivity Program has kind of helped us kind of move
20 along in a bunch of these efforts.

21 So this guy over here is the Oncomouse, and I'm
22 going to talk a little bit about what really goes on in
23 terms of the generation of scientific and technical
24 knowledge and how intellectual property rights influence
25 that, and this guy over here tells a lot of the story,

1 so when you think of the life of being a research mouse,
2 it's actually a pretty good life because you kind of get
3 whatever food you want. That's pretty good.

4 You get to play around with a bunch of other
5 mice in a little box, and they're never exposed to any
6 germs so these are pretty good things but this guy over
7 here, he's called the Harvard Oncomouse, and he was
8 developed at the Harvard genetics lab in the mid 1980s
9 in the laboratory of Phil Leiter and Tim Stewart, and
10 despite all those good properties of being a research
11 rat, this guy has cancer genes inserted into his DNA, so
12 that it's incredibly likely that he gets a variety of
13 different forms of cancer, so that's the bad part of
14 being a research mouse. You don't get the common cold.
15 You just die of cancer.

16 Now, the other part about this mouse is that
17 when you think about that, what kind of invention is
18 they, and that's going to be a very central point of
19 this talk? Because on the one hand, the development of
20 the Oncomouse is like a first order fundamental
21 scientific discovery because when you insert genes into
22 a mouse and give it cancer, you just discovered the
23 genetic basis for cancer.

24 At the same time, the same exact investment,
25 same exact social research cost, it's also a technology

1 because if you want to be one of the firms that Andrew
2 was looking at and other people have look at and you
3 want to screen thousands of potential cancer compounds,
4 boy these mice are pretty useful to figuring out drugs
5 are going to respond to different potential cancer
6 treatments.

7 So not surprisingly, very fundamental scientific
8 discovery was published in Cell, a very highly cited
9 paper in Cell. People start building and kind of using
10 the Oncomouse, and then what happens is a very
11 interesting kind of thing which is Harvard went out and
12 not surprisingly like many universities at that time,
13 they got a patent. They got a piece of formal IP, first
14 trained genetic mammal patent. This is going to make a
15 difference for the empirical strategy we're going to
16 use, but the patent actually comes four years after the
17 initial publication in the scientific literature.

18 By prior agreement the patent is licensed to
19 DuPont. DuPont's lawyers basically thinking about the
20 technological potential of the mouse basically starting
21 asking people for very -- basically saying if you come
22 up with -- if you're using our tool, I think it was a
23 tool almost like Microsoft Word, we write novels, but we
24 need the tool to get going. If you come up with a great
25 drug from this mouse, we need a 10 percent share of the

1 profits. You can easy actually see that on the one
2 hand, Bill Gates has never been accused of not knowing
3 how to make money. He also knows how to give it away
4 now, which is also good, but that would be as if J. K.
5 Rowling had to give back a royalty back to Bill Gates
6 because she wrote Harry Potter on Microsoft Word.

7 So on the one hand, more than that, right -- on
8 the one hand, there's this royalty that's going to be
9 involved, but they don't trust the scientific community
10 that is basically handing these mice back and forth to
11 each other like they're hot cakes. They say, if you
12 publish in the academic literature about they mouse,
13 guess what, you're going to have to have our lawyers
14 look at it before it goes out for review, and that
15 created a tremendous furor among pure academic
16 scientists, most of them funded by the NIH research,
17 which has funded this kind of mouse development for a
18 long time, who said, Oh, my goodness, this is really
19 going to stifle the free flow of ideas within the
20 scientific domain, which is the precursor at some very
21 deep level to a lot of the applied developments and
22 technologies that we've talked about today, okay?

23 That led to a very kind of long, detailed story
24 that Fiona has a truly beautiful paper about that kind
25 of details the history of this Oncomouse case study, but

1 ultimately what happens is the NIH knocks on DuPont's
2 door and ultimately say, By the way, I'm sure you've
3 noticed that DuPont has a lot of contract with the
4 government, and it would be really good if you let off
5 on the mouse a little bit because the scientists are
6 worried about it, and the director of the NIH made a
7 very specific effort to essentially lead to free and
8 open exchange through a place called the Jackson
9 laboratory in Maine. It's the largest mice research
10 facility in the world.

11 So what are some of the basic themes that that
12 kind of gets at? One is this very specific idea that
13 very often -- even just today, and I think even in
14 Michael's presentation -- I very rarely disagree with
15 Michael. He started to say there's sort of a basic
16 science and then we're going to develop the technology.
17 Very often in this area the science and the technology
18 come hand and hand, that a single discovery, once you
19 have this fundamental scientific insight, the technology
20 in some sense emerges. It's exactly the same
21 investment.

22 So we're going to be thinking about the role of
23 this dual knowledge. I think that's an important thing
24 for policy, for economics, for antitrust, for innovation
25 policy in this area. The second is we're going to do a

1 little bit of work in trying to evaluate a particular
2 idea that surrounds this conception of dual knowledge,
3 which is the anti commons hypothesis, that the expansion
4 of intellectual property rights somehow has kind of
5 stifled the free flow and the cumulateness of what
6 used to be public scientific knowledge, and the way we
7 are going to do that I've almost already kind of hinted
8 at is this kind of we're going to basically take
9 advantage of what we're going to call patent paper
10 pairs.

11 We're going to take advantage that the idea is
12 that you make a single investment, and on the one hand,
13 we you see it substantiated and embedded in the
14 scientific, and then we're going to see citations to
15 that paper, and then also at some future point in time
16 we're going to see a patent that's going to cover
17 exactly the same piece of knowledge that was covered in
18 the paper. Fiona, my coauthor, is a scientist by
19 training so she can kind of evaluate this at a deeper
20 level kind of really showing that it's the same thing
21 and we've developed fairly sophisticated algorithms at
22 that point to do that.

23 So essentially what we're going to be asking is
24 when a discovery has both scientific and commercial
25 potential, how does the IP impact the rate and direction

1 of scientific discovery and the ability for cumulative
2 innovation?

3 So kind of at a broad level I think -- this is I
4 just think a useful thing to kind of remember, back in
5 high school or something, at some point you kind of
6 learn that there's this thing called science,
7 understanding why kind of the Baconian ideal of science,
8 there's also this thing called technology that's kind of
9 recipes for how, and there's some relationship between
10 science and technology.

11 Science obviously provides new knowledge, new
12 tools, new research practices, even understanding the
13 social environmental impact of technology and basic
14 science. Global warming for the first 30 years was kind
15 of a hypothesis. It was a scientific driven exercise
16 that now we're thinking about the technological
17 implications of that.

18 Of course when you think of it for three more
19 president minutes, you say, Ah, technology also must
20 impact science as well, right, because of course science
21 itself has been dramatically influenced, right, by the
22 computer, by various research tools, by the mouse, but
23 of course it comes back and also raises a new and
24 fundamental question.

25 However, what we're going to try to emphasize,

1 and this goes back to a book written by Don Stokes about
2 ten years ago, is what happens when a good amount of
3 research that's being done, particularly publicly funded
4 or research that could be done in the public sector or
5 in the private sector on the margin is essentially not
6 this kind of very pure research of Neils Borg who
7 is kind of studying quantum psychics without any regards
8 for its application or like Edison, who just wanted to
9 build up GE as a company, so let's make things that work
10 with electricity creating the Edison effect at the same
11 time, but remember Louis Pasteur?

12 What was Louis Pasteur? Louis Pasteur was an
13 accomplished microbiology who was running around getting
14 research contracts with the French beer and wine
15 industry, and what the French wine industry really
16 worried about in the 19th century was why wine ferments
17 and what was the process, right, because they were
18 increasingly becoming famous for that and so and so
19 forth.

20 So Pasteur actually took his contracts in the
21 wine industry and he figure out he could get the second
22 contractor with the milk industry at the same time
23 because surely if you can figure out why milk went sour,
24 he could figure out why wine ferments, and he then was
25 setting a very applied industrial technology problem,

1 which of course if you really want to understand the why
2 wine ferments, why milk goes sour, why beer goes sour,
3 it would be really nice to have in the back of your head
4 the germ theory of disease. On the one hand, once you
5 have the germ theory of disease, it leads immediately to
6 a technological application, pasturization, but more
7 generally, you have just one of the most fundamental
8 scientific discoveries of the past 200 years, and the
9 same investment, privately funded, patent associated
10 with pasturization, seminal scientific papers associated
11 with this discovery.

12 In some sense I mean -- how much time do I have,
13 by the way?

14 So in some sense what Fiona and I have been
15 doing is -- let me go back.

16 So more recently people have noticed and sort of
17 emphasized particularly in the legal scholarship
18 literature and political circles around Washington,
19 within the FTC indeed, that intellectual property rights
20 might be having an impact, right, when you have this
21 kind of dual knowledge.

22 If you start covering things with intellectual
23 property rights, they might somehow impede scientific
24 progress, and it can happen in a bunch of different
25 ways. For example, it can just simply be that getting

1 -- there's so many different pieces of little knowledge
2 that you would have to license for in order to do your
3 marginal discovery, that just figuring out, contracting
4 with everyone and overcoming the transaction cost might
5 be quite difficult.

6 Secondly, there might be just pure kind of rent
7 seeking. So, in other words, people might be
8 essentially using their intellectual property rights to
9 shake their bargaining power. For example, of course
10 I'll let you have your mouse, let you use my mouse, but
11 I hear you have a really good graduate student, and I
12 would rather him or her work in my lab, so this sort of
13 horse trading over materials or their data over -- and
14 over people.

15 Indeed what we can see is kind of intellectual
16 property can actually have the impact of actually
17 limiting the cumulativeness and the process of
18 cumulative scientific discovery.

19 So just to be clear here, there are kind of
20 three basic mechanisms that you think might occur here.
21 One is strictly foreclosure mechanism, so even though as
22 a scientific piece of scientific research, you're
23 allowed to have access to my data and materials, I can
24 always then say, You know what, you're literally not
25 going to use it because I'm basically foreclosing you

1 because I have intellectual property rights around that.

2 Secondly, and this kind of particularly for
3 things that ultimately have some downstream activation,
4 you can imagine that all of a sudden you can sort of
5 start to stack royalties, so if there's only one input
6 supplier and they ask for ten percent royalty, I don't
7 think that would make that much of a difference on the
8 margin, but many of these technologies actually combine
9 20 or 30 different insights, and if you have to find a
10 license which all of those people and each of them is
11 requiring a 10 percent royalty, it becomes a little more
12 complicated.

13 Then the third is when the receipts are
14 dispersed, it's going to be hard to contract for that.

15 So in some sense what we've done in this
16 empirical project, which I'm going to describe in just
17 some brief level, is we're saying whether or not IP
18 raises the price of the research or somehow distorting
19 research choice, forcing people into alternative
20 projects, this kind of anti-commons effect which has
21 been raised up in the literature, suggests that IP is
22 going to somehow slow the diffusion of knowledge that's
23 produced in this quadrant.

24 What we tried do in this paper is really see if
25 we could find some sort of systematic grounding for that

1 that wasn't simply kind of one or two of these sort of
2 high profile cases such as the Brocca breast cancer gene
3 or the Oncomouse story I told you about earlier, so what
4 we did is we basically used this insight about these
5 patent paper pairs and the institutional features of the
6 publication and patent system to essentially create a
7 little bit of an experiment.

8 Essentially we collected a sample of research
9 articles that are at risk for patenting. Essentially
10 we went to the leading journal, it's called Nature
11 Biotechnology, and essentially this the journal, the
12 equivalent of the American Economic Review For Biotech,
13 okay? So it's -- this journal, if you read its
14 editorial mission, it basically talks about it's looking
15 for discoveries that are scientific in nature and also
16 have a technological component.

17 Then what we did us -- and when I say we I mean
18 Fiona, we divided -- this project was actually
19 completely helped by the fact that she was on bed rest
20 for three months with her first child, so she was able
21 to go laboriously through every single one of these
22 papers and look at the patent record.

23 We've gotten better over time at systematizing
24 this, but basically do the first auditing of how many of
25 these patent paper pairs are out there, so essentially

1 we went through basically -- and what that led us to do
2 was to go through an entire journal for three years,
3 look at 340 research articles, and it turns out, as I'll
4 talk about in a little while, half of the articles in
5 this journal are ultimately associated with intellectual
6 property.

7 Then what we do is we take advantage of this
8 absolutely fundamental feature of the difference between
9 how science and technology operate in the life sciences,
10 which is in the life sciences, scientific publication is
11 very, very rapid, on the order of weeks or months.

12 On the other hand, the patent grant delay as I
13 think there are many economists here, so I will say,
14 they take their orders from the RAND journal of
15 economics in terms of publication delay. The patent
16 office takes at least two years, if not three or four,
17 and before you get your patent rights, your patent
18 grant, you have no rights, and until 2001, the
19 applications were secret until granted, and the reason
20 you have no rights is the rights are uncertain until
21 they're approved, okay?

22 So essentially people could use this knowledge
23 that has been disclosed in the scientific literature for
24 several years, and then what's happening is that some of
25 the articles that we see get a little shock where all of

1 a sudden there's basically a patent grant. We don't
2 think the patent grant is itself the fact that you don't
3 have any effect on the scientific community, and I don't
4 think that researchers are kind of looking at the Patent
5 Gazette every Tuesday morning as it goes on the web.

6 I think instead what happens is university
7 licensing offices at that point start sending out MTAs
8 and nasty grams saying, if you want to use this mouse,
9 if you want to use this material, guess what, you're
10 going to need to -- you're going to need to get an MTA
11 or I'm going to charge you a high price or whatever they
12 say.

13 So what we're going to do is measure the
14 citation rate by follow on articles to each sample
15 article, and then essentially what we're going to ask
16 is: How does the granting of intellectual property
17 change the citation rate for each individual article
18 relative to what you expect given our sampling of
19 control, okay?

20 So how do we do that? So, in other words, how
21 does -- how does the citation scientific paper change
22 after a patent is granted, accounting for fixed
23 differences across articles and relative to the trend in
24 citation rates for articles with similar
25 characteristics? And a second thing that we're going to

1 ask is: When should this really matter? And in
2 particular you might imagine that if the article was
3 published and a published article comes out with three
4 researchers from Gen and Tech, you might say, You know
5 what, they probably have the rights already signed up,
6 if we're considering this as a research stream we want
7 to get involved in, actually we should go and license
8 with them right now.

9 On the other hand, if it's a bunch of university
10 researchers you might -- people put a lower probability
11 that there's intellectual property in that area, and so
12 the patent grant itself will have a bigger impact over
13 time.

14 So we have -- as I said we have the sample from
15 Nature Biotechnology. We have 340 initial papers. It
16 turns out 169 of those are ultimately associated with a
17 specific patent, and for each article and patent --
18 article and patent, we then collected detailed patent
19 and paper characteristics.

20 I don't know what help this is. This is kind of
21 fairly highly cited articles. They each get about ten
22 citations per year, so if you look at your own citation
23 rate for your own articles, you will say, Boy, I wish I
24 was publishing in Nature Biotech, and then basically
25 what we get is this kind of raw kind of thing that's

1 happening, and in the data, the pink line are those
2 articles that are ultimately associated with the patent
3 while the purple are the ones that are never associated
4 with the patent.

5 What you can see is the pink line sort of starts
6 a little bit higher, goes up until the years 2 and 3,
7 and then converges in the latter years and kind of as
8 it -- in the four or five years after publication
9 converges back down to the rate associated with the
10 purple line.

11 In other words, there seems to be something
12 that's happening relative to what's predicted by the
13 first few series in the sample to those in the pink
14 category, and the thing that's happening is in that
15 second, third and fourth year we're seeing a lot of
16 these patent grants.

17 So this is a negative binomial specifications
18 and these are incidence rate ratios, so you interpret
19 all those numbers relative to one, so 1.195 means 19
20 percent relative to what you would expect, and the key
21 kind of thing to look at is this patented post grant.
22 Those are essentially the decline relative to one that
23 would be associated with the reduction in the citation
24 rate relative to what we would expect.

25 What we do is a series of specifications, and

1 what you can see at least in these two that I highlight
2 is around 6 billion in the paper, but basically what we
3 see is is that there's a decline between about 10 and 20
4 percent in the citation rate.

5 What we see more specifically here, what we've
6 done is we've sort of looked at, Is there something
7 that's happening in terms of these articles in terms of
8 their citation rates before the patent is granted or
9 after the patent is granted? And you can see things
10 kind of bounce around? Prior to patent grant, there's a
11 little bit of effect, the year here the patent grants
12 but then things kind of go sour in a hurry, okay?

13 One more minute? So what I'm going to do is so
14 we have this kind of result summary. Essentially what
15 we find is that this matters, and so let me kind of just
16 take time for the conclusions, which is to say in some
17 sense, one important policy implication of this study is
18 that patenting does not seem as of yet to somehow have
19 fatally undermined the academic system.

20 What you're saying is you incorporate patenting
21 into essential the basic scientific research, and what
22 you're getting is essentially a tax on some of that
23 research which is reducing some citations for some
24 articles, but it's not like leading to an 80 percent
25 decline in anything, so it's modest relative to some

1 claims in the policy and the legal literature that
2 intellectual property is somehow undermining, fatally
3 undermining academic research.

4 However, with that said, within the quadrant,
5 the increased use of formal IPR seems to be
6 significantly shaping the structure, conduct and
7 performance of both university and industry researchers.
8 There is a reduction in the use of knowledge that is
9 going patented, and we have a sort of follow on paper
10 where we really sort of show that there are margins that
11 are changing.

12 For example, we see an increasing number --
13 after the patent is granted an increasing number of the
14 articles are collaborations rather than independent
15 citations. In other words, what used to be a citation
16 is now being turned into a co authorship, okay?

17 There's also a decline in the quality of the
18 articles and it's particularly concentrated in public
19 sector researchers. More generally patents turn out
20 simply to be not just a legal document. Within some
21 seamless web of cooperation, scientists are very
22 strategic actors all by themselves, even without
23 patents, nor are patents bludgeon to stop scientific
24 progress.

25 Patents seem to be a change and being

1 incorporated into the rules of the game for a very
2 important part of scientific exchange, cooperation and
3 credit, and I had one more slide but like Andy, I'll
4 hold off on that.

5 (Applause.)

6 MS. HOSKEN: Thank you. We have Loren Smith to
7 discuss the paper.

8 MR. SMITH: So I am going to be very short. I
9 don't have -- unfortunately for Scott, I don't have a
10 lot are substantive -- I have a few comments that are
11 kind of easy comments to make about work like this, and
12 I have a few suggestions for how he might be able to
13 test the robustness of his results but I don't have any
14 real landmark things that are going to help you out, but
15 I will -- so this is kind of the anti-commons effect
16 he's trying to capture.

17 If you had two article -- let's say you had the
18 same article in two different worlds, one world where
19 there are no patents, and the other world where there
20 are patents, he's trying to measure what difference
21 there would be if there were a patent at period T, in
22 the citation rate of that article, and what he's going
23 to try to use for the red line or to proxy the red line
24 is a set of articles that don't receive patents that are
25 very similar to the articles that do receive patents so

1 he's doing a difference in differences in the number of
2 citations that these articles receive across the two
3 spheres.

4 So he addresses citations on article and year
5 fixed effects, age a dummy variable equal to one in the
6 patent grant year, and a dummy variable equal to one
7 after the patent, dummies for the years after the
8 patent.

9 And the key results he finds in this paper are
10 that patented articles are associated with a 10 to 20
11 percent fall in their expected citation rate, and that
12 the effect -- another key result is that the effect is
13 more pronounced when the article is written by public
14 authors, so he attributes this effect to the fact that
15 maybe authors in the public sector are not as aware of
16 the patenting procedure, so it's more of a surprise to
17 them when the patent comes into effect, and therefore
18 there's a more pronounced effect after the patent,
19 excuse me.

20 There are -- he also mentions some alternative
21 hypotheses for why that might occur to be fair, but you
22 know, it's hard to know exactly why you would get that
23 effect.

24 So my discussion, first difference in
25 differences is appropriate when the treatment is random,

1 so this is a common criticism of difference in
2 differences using natural experiments, but it seems to
3 be particularly problematic here. The patent doesn't
4 seem to be something that people wouldn't anticipate or
5 he also mentions in the article that he needs at least
6 some of the people to be surprised by the patent, and I
7 think in general when you do difference in difference
8 analysis, you want all of the people to be surprised by
9 the event.

10 He controls for differences in level of
11 citations across articles, but assumes the change in
12 citations over time is the same for all articles in the
13 absence of a patent so basically he's assuming that the
14 decline in patents for the two different groups is the
15 same in the absence of the patents. The citation
16 patterns are the same patented and unpatented articles.

17 He tries to evaluate whether this effect is
18 salient or not by doing a similar analysis using only
19 patented articles, exploiting the difference in the
20 timing of the patents. He does get a similar result
21 when he doesn't include fixed effects, but when he puts
22 the fixed effects for -- article specific fixed effects
23 into the regression, the result disappears or at least
24 there's no significant effect.

25 You're frowning.

1 MR. STERN: No.

2 MS. SMITH: So some other things he might do to
3 test the robustness of this assumption that the patterns
4 are the same for patented and unpatented articles is
5 perhaps see if there's a difference in the citation
6 patterns for patented and unpatented. He has this
7 period of time when no article is patented, so like
8 there's maybe a two-year period when none of the
9 articles in this sample are patented.

10 If the patent is truly the thing that matters in
11 the citation rate, then you can see if there's a
12 difference in the citation patterns with patented and
13 unpatented articles prior to patenting, so in that two
14 period when there is no patent.

15 Also if you could find another control group and
16 check to see if you find the same group, that's an
17 unsatisfactory comment because I don't have a good
18 control group for you to test this alternative against,
19 but that might be something that you would do.

20 In addition, the citation patterns in this --
21 so he's assuming that the level changed in the citation
22 period over time is independent of the level that they
23 start at, so he finds that patented articles are cited
24 more often than not patented articles, but he assumes
25 that the decline in their pattern would be the same in

1 the absence of the patent so he assumes that the pattern
2 is independent of the level.

3 You can see if the pattern of decline is
4 actually -- and this could go either way, right. This
5 could be that articles that start really fast also build
6 on each other and have more citations or it could be
7 that they fall off faster. You mentioned this in a
8 footnote, but this could make your result go either way.
9 It could be more of an effect or less of an effect
10 depending on what you find here.

11 Finally this is probably -- there's nothing you
12 can really do this comment, but what are the policy
13 implications? Are patents issued on intellectual
14 property bad? And you can't say anything about that
15 based on this article because of the point that I bring
16 up in the beginning, that this have not a random event.

17 People do not select into doing this research
18 not knowing that they're going to seek a patent, so they
19 might -- so if you wanted to evaluate the effect of the
20 patent on future research, you would have to say that
21 all of those articles that were published that
22 eventually received a patent would have been done in the
23 absence of patenting, and you can't possibly say that in
24 this case, so you can't measure whether this is a good
25 or a bad thing ultimately.

1 That's it.

2 (Applause.)

3 MS. HOSKEN: Scott, do you have any response?

4 MR. STERN: Thank you for those very thoughtful
5 comments. The only thing I would say is I would
6 slightly disagree with I didn't have time for it, but
7 when we only used the patented articles and exploit the
8 patent timing, so the fact that some articles get a
9 patent, some after two some after three, some after
10 four, there's an issue with basically foreign authors,
11 just how long it takes them to get a patent. They
12 clearly follow a different trend.

13 We are able to have one, if I'm not mistaken in
14 the final version, in the version that we distributed,
15 has roughly the same coefficient, like 11 percent or
16 something decline, looking at either the U.S. authors or
17 the public sectors author or the U.S. and public sector
18 authors, but it is true that when you include the
19 foreign, when you include the foreign private authors,
20 it does get more noisy, and that's just clearly a
21 different time pattern of the citation, but besides that
22 relatively small effect, that was very thoughtful
23 discussion.

24 MS. HOSKEN: And I believe we may have a few
25 questions in the back? Could you state your name first

1 and then you question.

2 MR. GILMAN: Dan Gilman. I guess I'm wondering
3 about a doctor's waiting room problem, which imperfect
4 magazine do you pick up off the table? So you've got
5 this domain that you're studying and you focused on this
6 journal. We start with the August nature journal and we
7 have a bunch of spin offs, Journal Nature, et cetera, et
8 cetera. We start with the Biotech Journal, we ever a
9 population of articles, and one subset is publications
10 that result in patents and what happens in citation
11 frequency and drop after patent, and the other is
12 articles that don't result in a patent or at least
13 within the time we're looking at don't result in a
14 patent.

15 And I'm wondering if that's the ideal contrast.
16 If the journal is designed -- these are -- this is a
17 highly selective journal. It's a highly selective
18 journal designed to look for biology articles of a
19 particular sort, namely ones quite likely to result in
20 patented products. Is the contrast class just failures?
21 Would we get different results if we looked at the
22 Journal Nature as a baseline?

23 MR. STERN: So that's a super question. I mean,
24 that's a super question. There's a lot in it. The
25 first point is I fully agree with you. We picked this

1 journal on purpose so that all the articles are
2 essentially potentially patentable, so we asked a lawyer
3 to basically look at the unpatented articles and say,
4 are they likely to be patents, and there's a literature
5 that I think that sort of describes it.

6 In substance the reasons things get patented or
7 not when they're like this kind dual knowledge often
8 depends on the idiosyncratic institution features of
9 where the research was done and things like that. I
10 think that's a true phenomena.

11 I am sure first that the rate of patent paper
12 pairs is much lower than in most other journals. We do
13 have some other projects as to however you look at --
14 and Fiona has a paper for example that came out in
15 science earlier this year where effectively you look at
16 the human genome, 23, 24 percent of all genes,
17 regardless of how well we know their application, even
18 if we know very little about them -- 23, 24 percent have
19 a patent on them, and many of those will be associated
20 with almost all gene discoveries or any version of
21 function are going to be published in relatively high
22 quality, either in Nature Genetics or in Nature or Cell
23 or something like that.

24 So I guess what I would say is I would fully
25 agree with what you said. We have basically very little

1 idea about how much research is essentially insulated --
2 so we spend a lot of money on life sciences research,
3 spend a lot of time in private R&D investment, and we
4 have very little idea of how much is essentially
5 insulated from intellectual property concerns and
6 commercialization, basically pure scientists get with
7 NIH degree or Howard Hughes grants, doing stuff just
8 because they're doing it.

9 How much time is this kind of collision of dual
10 knowledge and how much is very applied research that
11 could never be published in the traditional literature?
12 And Pierre Azoulay had some very very nice work that
13 thinks about the determinants of faculty patenting
14 behavior and tries to do that a little bit more -- he
15 would have a much better answer than I would thank you.

16 MS. HOSKEN: I think in the interest of time, we
17 will move on to our panel which will hopefully continue
18 to discuss some of these issues so I can have my panel
19 discussants please come up.

20 (Pause in the proceedings.)

21

22

23

24

25

1 PANEL: PHARMACEUTICAL R&D AND BIOTECH DEVELOPMENT.

2 MODERATOR: LAURA HOSKEN (FTC, BE)

3 SUZANNE MAJEWSKI (DOJ)

4 JIM BARRETT (NEA)

5 GERALD QUIRK (Infinity Pharmaceuticals, Inc.)

6 PETER RANKIN (CRA)

7

8 MS. HOSKEN: So our first discussant in the
9 panel is Sue Majewski, I hope I'm pronouncing that
10 correctly, from the Department of Justice, our sister
11 institution.

12 MS. MAJEWSKI: I'll do my best to use this
13 microphone. I'm going to try to talk without this
14 microphone. And before I start talking at all, I have
15 to do the standard disclaimer that anything I say are my
16 views and not the views of my agency, and certainly I
17 want to thank the FTC for inviting me here in what I
18 hope is a great follow on talk to some of the subject of
19 the wonderful paper by Scott Stern and Fiona.

20 So the type of this talk is: "Will patent pools
21 solve the tragedy of the anti-commons in life sciences,
22 (if there is a strategy of the anti-commons in the life
23 sciences)."

24 So what I want to do is sort of paint a picture
25 of talking about the issue of the tragedy of the

1 anti-commons and the debate that's been circling around
2 it and the extent to which patent pools may or may not
3 solve some of these problems.

4 In a 1998 issue of the Journal of Science, law
5 professors Michael Heller and Rebecca Eisenberg
6 forecasted that the proliferation of patents in the
7 biopharmaceutical industry was likely to cause a radical
8 reduction in R&D, and unlike the story of the tragedy of
9 the commons where you have a story where nobody has
10 property rights over the commons, nobody has the right
11 to exclude anyone from using the commons, as a result
12 all the farmers let their cattle go graze in the commons
13 and it results in over grazing, over use of property
14 because there is no right to exclude, Heller and
15 Eisenberg instead coined the phrase tragedy of the
16 anti-commons, and their idea was for example in the
17 biopharmaceutical industry, if you have too many rights
18 to exclude too many patents at this upstream level,
19 might that cause an underuse of property at the
20 downstream level because there are too many people
21 demanding rents at the upstream level and blocking the
22 potential commercial value of the downstream.

23 And a question then arises if you believe this
24 might be a problem as to why you have an industry where
25 money is left on the table, you've reached this

1 inefficient equilibrium and money is left on the table,
2 deals are not being done, and R&D -- potentially
3 profitable R&D downstream is not being undertaken
4 because you've got people debating the value of what
5 this upstream rights should be, and there are plenty of
6 examples in a history of industries working to try to
7 get around the problem of fragmented rights held by too
8 many rights owners.

9 Copyright collective organizations and
10 copyrights such as Ascap collectively address issues of
11 multiple rights held over music distribution and music
12 publishing? Professor Peter Munsell -- not Peter, Rob
13 Burgis has talked about other collective rights
14 organizations such as Water Basin Authorities where the
15 idea is you have a river going downstream. You've got
16 multiple cities and jurisdictions which have rights over
17 the river and the water. Your city is at the bottom of
18 the river, and how can you contract with everybody
19 upstream to make sure you have water at the end of the
20 day.

21 And then of course patent pools -- actually I
22 was surprised when I started looking around that patent
23 pools have existed since certainly the late 1800s.
24 There have been tons of industries that have enabled
25 patent pools, and going back to National Harrow, which

1 was the first legal case in 1902 dealing with the patent
2 pulling, the question is: Can biopharmaceutical
3 industry find an institution like patent pools to sort
4 of solve this problem if it exists?

5 So before I go on, because I thought someone in
6 the audience might not know what a patent pool is, I
7 want to describe what patent pools are. These are
8 individual institutions or organizations to which firms
9 contribute their intellectual property. They license
10 their patents to the pool. The pool then turns and
11 assembles this bundle of IP rights and licenses the
12 whole packages to the downstream licensees.

13 And the way in which the Cornell problem can be
14 solved, which Scott talked about a little, you have a
15 problem of stacking royalties, this double
16 marginalization problem, could in theory, in economic
17 theory end up with a result where the final licensed
18 price to the downstream user or drug developer in our
19 case could end up being higher in the event you have
20 this double margin problem happening with lots of firms
21 than it would happen if the pools established what was
22 effectively like the monopoly price, and in fact the
23 patent pool establishing a monopoly upstream could still
24 end up having a lower royalty rate than would happen if
25 the rights were fragmented across all kinds of

1 organizations.

2 The DOJ has reviewed four patent pools within
3 the last maybe six or eight years. All of them have
4 been in the IT sector. The MPEG LA patent pool in video
5 compression, two DVD pools and one in 3 G telephony, in
6 each case we issued a business review letter describing
7 each of these patent pools, and the terms of those
8 pools, what we thought gave us comfort that there wasn't
9 an anti-competitive problem, and what facts perhaps if
10 they were changed might cause us concern that there
11 would be an anti-competitive problem in forming patent
12 pool.

13 So in recent year, over the more than a hundred
14 years that there have been patent pools in existence,
15 antitrust agencies have taken a more positive view or a
16 more dim view over the years, but in recent years we've
17 done sort of more permissive and subject to a lot of
18 caveats that are in these business review letters, in
19 particular that the pools don't contain substitutable
20 technologies, so you don't want a patent pool that
21 contains all the patents for the blue mousetrap and all
22 the patents for the red mousetrap.

23 So then the question is can or will the
24 biopharmaceutical industry form patent pools? Now,
25 Heller and Eisenberg took a very dim view of this in

1 their article, and they cited in particular high
2 transaction costs in getting these rights holders to
3 negotiate and decide how the patent pool should be
4 formed and who gets what for license fees, and they
5 cited heterogenous rights holders, and in particular
6 that there's a lot of universities who have patents, and
7 maybe it would be more difficult to have the for profit
8 and the non profits sector agreeing, and cognitive
9 biases, the sense of nobody being able -- most people
10 who a patent may think it's much more valuable than it
11 really is.

12 Now, one of these reasons why they say patent
13 pools may not be appropriate in biopharmaceuticals
14 really answer the question of: If all of these factors
15 are true, that doesn't make patent pooling any more
16 difficult than bilateral licensing negotiations, and in
17 fact -- and on some of these in fact for example,
18 heterogenous rights holders, in fact universities have
19 been members of patent pools in the IT sector, so that
20 doesn't seem to be a hold up earlier.

21 I'm kind of running out of time, so I did a
22 search on the web and through various academic journals
23 to try to find examples of patent pools that have been
24 formed in biotech, and I came across four that I can
25 solidly identify. Of these, only the green fluorescent

1 protein patent pool was sort of what I thought of as
2 comparable to the pools that we've seen in other
3 industries.

4 This patent pool has numerous IP holders who are
5 for profit firms. People are snickering in the
6 background so maybe people know more about this than I
7 do. The Golden Rice story seems to be far more
8 motivated by political reasons, the Ag industry wanting
9 to showcase that genetically modified rice or the
10 genetically modified crops were a good thing so they
11 kind of agreed to pull these patents and license the
12 stuff at a very low rate.

13 The technologies patent pool seems to be really
14 more like a process agreement, and in the last case of
15 proposed essential patent pool for AIDS which was
16 something that was shepherded by the UK government.
17 It's an example of an attempt of government intervention
18 to try to get industry to agree to a patent pool, but I
19 haven't found any evidence that it was actually worked.

20 So then the question is: Are there other
21 industry solutions to fragmented rights, and in the lack
22 of time, I'll just mention a wonderful paper by Walsh,
23 Arora and Cohen talks about other solutions in this
24 industry. They have a great survey evidence on how
25 firms deal with fragmented rights, and they actually

1 come to the conclusion that they don't think there's an
2 anti-commons problem in the industry at all.

3 Certainly people like Rod Burgis has talked
4 about the solution of putting IP in the public domain,
5 and that's this idea of preempting upstream patenting by
6 patenting it first and putting it or discovering it
7 first and putting it in the public domain where it's
8 known broadly and widely, and therefore no one else can
9 copy it.

10 And the SNB consortium, there's a now a tomato
11 SNB consortium that I found in the Merck Gene Index,
12 which are all examples of putting the IP in the public
13 domain.

14 Just to wrap up because I know I'm out of time,
15 it seems to be in my review that anecdotal evidence is
16 thin on biopharmaceutical patent pools patent. I had a
17 hard timed finding any, so the question is: Well why
18 haven't they been occurring? One thing is in a number
19 of these recent patent pools that the DOJ has had
20 business review letters on, they've all involved
21 intellectual property -- well, they've all involved sort
22 of the IT industry where there's a standard that they
23 are trying to contribute pools to a particular standard
24 that was formed by a standard setting body.

25 And certainly in biopharmaceutical you don't

1 have the standard setting scenario going on, and one
2 question is whether it's just that there's too much
3 unsettled IP rights in terms of litigation right now.
4 Certainly in ag-biotech, my impression is that's the
5 case. I don't know it for a fact, but it seems like
6 there's a lot of litigation going on and sort of
7 understanding the landscape and how it's going to play
8 out, and a question of what patents would be essential
9 to practice a downstream invention at the end of the
10 day, essentiality being one of the terms that we use in
11 the business review letters for what does or does not
12 belong in the patent pool.

13 Bilateral cross licensing, again Walsh and Cohen
14 and Arora seem to find that it's common, a question of
15 whether public domain strategy is useful or working and
16 is it too soon to tell?

17 There are several people here in the audience
18 who are from the industry, and maybe they have a better
19 perspective on this than I do, but as for now, my sense
20 is that patent pools are not all that alive and well in
21 this industry, and it's a good question and as good
22 avenue for future research why this might be the case.

23 (Applause.)

24 MS. HOSKEN: Thank you, Sue. Our next speaker
25 is Jim Barrett from NEA, and that's not the National

1 Endowment for the Arts. It's actually New Enterprise
2 Associates. I'm sure he gets that joke all the time.

3 MR. BARRETT: Actually the other joke is they
4 wonder why someone from the teachers union is talking
5 about innovation. So that's the blue NEA. I'm the red
6 NEA.

7 So what I thought I would do is spend -- F 7 or
8 5? I thought I would spend a few minutes sort of
9 telling you what venture capital is all about because I
10 think it's important to understand exactly what we do
11 and why we do it. I mean, the discipline has a certain
12 amount of bad reputation in certain circles, mostly with
13 entrepreneurs because we can be pretty neat on
14 valuations. I'll try and give you a sense of what we've
15 done.

16 I think along with that context, you'll see what
17 drives us as an important component of innovation.
18 Particularly in biotechnology you'll see why we do what
19 we do. Let me just start here.

20 Venture capital is the perfect other people
21 money, other people's money guy. We invest other
22 people's money. We do have to contribute a little bit
23 to the partnership, about 1 percent, but it generally
24 it's other people's money. Our job is to manage the
25 firm, to invest the money.

1 Typically in our business, in the early stage
2 and in rapidly growing companies, it's a major source of
3 innovation for the industry, and what we try to do in
4 the end, the only way we can win this game is to invest
5 in and help develop sustainable businesses that
6 eventually can become self-sustaining either through
7 reader through an IPO eventually or more frequently now
8 with a merger opportunity.

9 So someone says is liquidity a life saving
10 event? It is for me because if I don't get liquidity, I
11 can't raise my next fund, and I have to go back to
12 academics, and that's a poorly paid business.

13 So let me just -- the relationship among the
14 various players in the VC businesses is a set of limited
15 partners, generally institutions, pension funds of one
16 kind or another, endowments. Those are the major
17 contributors to the venture capital pool.

18 As a general partner we manage that pool. I'll
19 say a little more about that in a second, and we use
20 that pool to invest in portfolio companies, a pretty
21 straightforward knowledge. As I said the sources of our
22 funds are people we know and love. Many of you are
23 probably venture capitalists by one or two removed if
24 you have a pension fund or an investment in a mutual
25 fund, they often are also investors in those.

1 The objective, the reason LPs invest in venture
2 capital partnerships is because at least in principle,
3 these funds have superior returns compared to other
4 investments, so particularly treasuries, even the stock
5 market. I know or I'm sure that a lot of you are
6 economists, you appreciate this, that in a properly
7 diversified investment pool, it's sort of
8 counterintuitive that even though an investment in
9 venture capital is a much more risky standalone to most
10 other investments in the portfolio, it turns out because
11 the returns are disproportionally higher, the aggregate
12 risk reward potential of that pool is greater with a
13 venture captain investment than without it.

14 That's why people come to us to balance out
15 their to their portfolio among the unusual elements of
16 stocks and bonds, it turns out the portfolio return
17 better at lower risk with a relatively small proportion
18 of their investment in private equity and venture
19 capital at the end.

20 Venture capital firms are not one trick ponies.
21 Sometimes people think we take a chunk of money, invest
22 it, reap the rewards and move on, but in our case, for
23 example, we are investing through our 12th fund. We
24 just raised 2 and a half billion dollars of commitments
25 this spring, so in order to stay in business as an

1 enterprise, we have to hopefully over the long-term
2 deliver the kinds of returns that LPs expect from us.

3 Our job has really two essential components to
4 it when we're said and done. The first is to identify
5 worthwhile projects, worthwhile benefits, science,
6 technology and markets, and secondly is to do diligence
7 on those investment opportunities. If we get our
8 diligence wrong, we're going to fail every time, so we
9 spend huge amounts of time trying to understand what are
10 the risks and the opportunities for any given
11 investment. If we fail there, then we're out of
12 business.

13 In any case we're a very active management
14 group, so we're not passive investors. We're not
15 financial manipulators. We make an investment, and the
16 company will take board seats in almost every case, and
17 our intention there is to influence the trajectory and
18 outcome of the company, so we generally view ourselves
19 as assets to the entrepreneurs rather as they sometimes
20 think we are pains in the neck.

21 The end of the story though is eventually we
22 have to create value through that investment, analytical
23 and support process, and that value is realized either
24 in IPOs where the stock becomes liquid and we can sell
25 it into the market at some point. Generally we had --

1 our ownership positions in these companies is
2 sufficiently large that it's hard for us to deal with
3 thinly traded stocks so oftentimes we find it necessary
4 to maintain our investments years beyond the initial
5 public offering, and in fact in the current environment,
6 IPOs are another liquidity -- sorry, another financing
7 event rather than a liquidity event.

8 To that point, let me go back to the beginning
9 here, there are just two sort of data slides, I've been
10 really impressed with the data slides I've seen here
11 today. We are in a difficult liquidity environment for
12 early and mid stage biotech companies, so this sort of
13 makes the point for the period of the companies that
14 went public in the '04-06 period, and the number I want
15 you to look at very carefully is the amount of money
16 raised prior to the IPO, in those companies in that
17 period.

18 And that's \$110 million, which is a lot of money
19 historically for private equity to put into these
20 companies. Sort of prototypical biotech success in this
21 area is a company called Metamune, and that company
22 raised a total of \$6 million before they went public.
23 Now we're having to put syndicates together that can
24 raise \$110 million before the companies go public. As I
25 said, even then we don't necessarily get liquid, and

1 we'll have to say in that investment for a fairly long
2 period of time, in the same vein, the time to liquidity
3 is getting longer, six and a half years from the initial
4 investment until the IPO is done, and again, it's not
5 necessarily liquidity then.

6 The second slide sort of states the obvious but
7 does have an effect on our investment strategy. It
8 turns out if you manage to get into a deal early, you
9 will do much better than if you get into it late, but
10 the flip side of it is you are in those deals for a very
11 long time before you realize any liquidity, so the
12 bottom line here is that as the size of the syndicates
13 have gone increasingly large to support projects for a
14 fairly long period of time, that means we can do fewer
15 than them, so if you're putting a hundred million
16 dollars into a project rather than ten, essentially
17 you're going to do 90 percent fewer projects.

18 In fact we're seeing there's a terrific squeeze
19 on early stage investment by entrepreneurs, and they're
20 having a difficult time raising money. I don't know if
21 there's a solution that the FTC can apply to that, but
22 in the current environment, because we are investing
23 larger sums and fewer deals, less innovation is being
24 supported at least in this time frame by venture capital
25 organizations. Thank you.

1 (Applause.)

2 MS. HOSKEN: Next speaker is Gerald Quirk who is
3 from Infinity Pharmaceuticals.

4 MR. QUIRK: While she's setting that up, I'm a
5 lawyer, not an economist, so there are no numbers or
6 Greek letters in my slides. I was actually getting
7 nervous trying to go back to college and how poorly I
8 did in economics in college and seeing as it's been a
9 great discussion I participated in so or listened to so
10 far.

11 I want to talk a little bit about licensing and
12 mergers and acquisitions as a way to kind of get from
13 idea to drug, and obviously the challenge for biotech is
14 that it costs \$802 million, I've heard a billion
15 dollars, but it costs a lot of money and it takes a lot
16 of time to bring something from idea to the market, and
17 that time frame is also longer than Jim and his
18 colleagues in venture capital are generally interested
19 in staying in an investments

20 So biotech companies like Infinity have to think
21 about partnering and buying or selling in order to bring
22 these drugs to patients.

23 Before I begin, let me also give the disclaimer
24 that I'm speaking for myself, not for Infinity, my prior
25 employer who is well known to the agency for better or

1 for worse, or for the biotech or pharmaceutical
2 industry. This is my own musings on the subject.

3 So I wanted to talk a little bit about who
4 Infinity is, and I've now been there for a little over a
5 month so this is a little bit of a test for me actually
6 putting the slide together, but part of why I did it is
7 not to sell the company but because it's kind of a case
8 study in biotech, so Infinity is a small molecule, drug
9 discovery and development company, and like many biotech
10 companies it was founded on the basis of a platform
11 technology that it licensed from academia, and in our
12 case it was a technology out of Harvard that enabled the
13 synthesis of natural product like compounds, so things
14 that are found in nature that may have therapeutic
15 benefit but can't be engineered into a drug for whatever
16 reason, chemical reason, and I know less about chemistry
17 than I do about economics.

18 But they licensed that technology and used that
19 as a platform for two things: One is to raise money by
20 doing transactions with large pharma, like Novartis and
21 J&J or large biotech like Amgen to help them design
22 compounds around targets of interest, but also to use
23 that technology to fuel our own internal drug discovery,
24 and as part of that we have two programs, one in the
25 clinic and one in preclinical development, both of which

1 are now partnered with a company called Metamune where
2 Jim is on the board somewhat coincidentally based here
3 in the D.C. area.

4 What those partnerships have done, the Metamune
5 partnership is, one, provided a significant amount of
6 cash to the company to be able to fuel development, and
7 at the same time it added capabilities. As a 110 employ
8 person company, having a robust clinical development
9 group or being able to commercialize something ourselves
10 would prove to be quite difficult itself, so having the
11 Metamunes or the Norvatises working with us to bring our
12 drugs to patients is critically important.

13 The other thing that Infinity did that has
14 become a little more common in the industry, instead of
15 doing a traditional public offering, it actually engaged
16 in an M&A transaction to do it, so last month Infinity
17 merged with a company called Discovery Partners
18 International, which essentially at that point was a
19 shell, a public shell that had about \$78 million in cash
20 on the NASDAQ listing. Infinity issued stock to their
21 stockholders.

22 Rather than selling them to underwriters who
23 would then sell them into the market, we sold those
24 shares to Discovery Partner. Shareholders generated
25 about as much cash as we would have in an IPO and then

1 was able to enter the public markets with the hope that
2 with the liquidity that comes from that we would
3 continue to be able to fuel our discovery engine and
4 using that platform, develop new drugs.

5 Long-winded I used half my time on just the
6 introductory slide, but that touches on a couple reasons
7 why biotech or pharma companies merge.

8 A lot has been talked about big pharma, big
9 products going off patent and needing to utilize
10 capacity, how to utilize people, meet revenue challenges
11 going forward. That's certainly the case for large
12 biotech. It could be a make buy decision. If you want
13 to enter a new market, new disease area, it may be
14 easier to buy that rather than develop that internally,
15 and for like a small company like Infinity, it's
16 accessing resources, and also small companies can be
17 buyers as well, and to do that, to mitigate portfolio
18 risk, if you have a one in ten shot of your drug that
19 just entered human clinical trials that is actually
20 going to be a drug, there's a significant amount of
21 portfolio risk, so the more shots on goal, if you will,
22 would be helpful.

23 So these transactions can take lots of forms and
24 out right acquisition, those where you're going to get
25 leverage from that by combining the organizations. You

1 can have a stand alone entity, and there's a lot of talk
2 where I am about big pharma wanting to come in have a
3 Cambridge research arm of the company and has people
4 kind of scratching their heads, but certainly stuff like
5 that happens.

6 You can have a purchase of a majority stake.
7 The Roush and Genentech example is probably the best
8 known of those or you can have a product specific
9 development commercialization license -- alliance which
10 basically could be the acquisition of a product and
11 joint development, many of which -- well, much of the
12 time the last one would also fall within kind of a
13 Clayton Act and make its way down here.

14 Regardless of any of the purposes for this or
15 the structures of it, it all comes down to the same
16 thing from an industry perspective. You want to get new
17 and better medicines to more people as quickly and
18 efficiently as possible.

19 Are we successful in doing these deals in
20 delivering them on that objective? Theoretically, they
21 all should. In practice, they don't always. That
22 doesn't happen, so I did a little bit reflecting and did
23 some reading in terms of whether or not you can predict
24 whether or not a particular type of transaction, size of
25 transaction, motivation for transaction is more or less

1 likely to advance that objective.

2 And I think the answer so that is probably not,
3 and give a couple examples of this from my prior life.
4 The M&A transaction I did, similar size, similar
5 motivations for maintaining -- aside from senior
6 management, really all the R&D and manufacturing and the
7 light stayed in another location and which ones worked
8 and which ones didn't, and some did and some didn't.

9 It was -- I'm try trying to control for things I
10 couldn't really get a hook on that. In a couple of
11 these, we've had where they're local, complete
12 integration of R&D groups working together in a single
13 location. We've had situations where you've got two
14 geographic disparate R&D groups with kind of comparable
15 platforms for the -- in the same space, and the
16 technology that came from each of those sites
17 contributed to line extensions and improvements on the
18 products that came from each of the constituent
19 companies. That happens.

20 So I was scratching my head trying to come up
21 with some sort of hypothesis on this, and I think where
22 I kind of came to, and it may not be a satisfactory
23 answer to people who tend to be kind of quantitative in
24 the way they think, is really it's qualitative. In
25 order for these things to be successful, for there to be

1 efficiencies or spillover, which a term that was
2 unfamiliar to me until a couple weeks ago, it's human.

3 It's ultimately how aligned are the constituent
4 parties to a transaction in terms of bringing together
5 capabilities and technologies to bring those drugs to
6 market? How can you overcome some of the kind of
7 culturally differences in the biotech or pharma, large
8 versus small molecules, focus on broad markets like
9 cholesterol versus orphan diseases, an entrepreneurial
10 culture that you'll get in a smaller company versus the
11 big business of pharma company.

12 I think it really comes down to how well it's
13 managed, how well it's integrated, and really alignment
14 in terms of how are we going to bring those companies
15 together and bring those products because ultimately if
16 you've got a research arm somewhere, whether it's local
17 or 2,000 miles away, if they're not on board with the
18 research program, the objectives and the, like those R&D
19 efficiencies are just not going to happen.

20 So in my 30 seconds left, kind of just as it
21 kind of takes a village to raise a child, it takes
22 actually a whole industry and interdependence in order
23 to bring a drug to market, and M&A and licensing
24 transactions are just a manifestation of that, and kind
25 of technology or IP is kind of useless. Freedom to

1 operate under patents is kind of meaningless unless you
2 have kind of management buy in and clear objectives in
3 those -- as a result of those transactions.

4 So deals work, not all the time, but this is a
5 way to really kind of overcome both a lot of the capital
6 and IP issues that could affect drug development
7 ultimately, so I'll leave it at that.

8 (Applause.)

9 MS. HOSKEN: Our last panelist is -- I should
10 say our final panelist is Peter Rankin from Charles
11 River.

12 MR. RANKIN: I would like to Chris Adams for
13 sneaking a consultant onto the schedule. For those of
14 who you do not know CRA, we are both a litigation and a
15 business consultancy, so my role here today is largely
16 to speak to some issues that we've come across in those
17 particular types of engagements.

18 In particular on the litigation side we often do
19 intellectual property disputes or evaluate the effects
20 of potential consolidation so which means we're either
21 over here or at the DOJ as friends or perhaps as
22 interested parties, and on the business consulting side
23 we do some work with assisting firms that are wrestling
24 with the potential effects on innovation that some of
25 these industry events will have. So like the DOJ, a

1 little bit longer, I speak for myself, not for CRA nor
2 any of our previous clients except for those who want me
3 to and we'll get to one of those in a second.

4 But just a little bit of general background
5 first. Thinking of this from the manufacturer
6 perspective of what are they considering when they think
7 about innovating going forward? We've got a volatile
8 environment in which to make investment decisions, and
9 these are all some of the most basic concerns that a
10 pharmaceutical manufacturer, whether biotech or
11 traditional pharma has do deal with, and the point that
12 was raised earlier today is these are all global
13 reimbursement. When a manufacturer decides to peruse a
14 particular route of research, they're not looking at
15 U.S. revenues.

16 In fact U.S. revenues are a decreasing share of
17 the total revenues for a project, so developments like
18 reference pricing in Europe are increasingly affecting
19 the portfolio decisions made by pharmaceutical
20 manufacturers.

21 Similarly, regulatory structure, biotech in
22 particular has a very, very difficult time getting
23 reimbursed in Europe. Most of the therapies that may
24 not have unencumbered access in the U.S. are often
25 second, third, fourth end line therapies in Europe.

1 Take Receptin, for example, which is a very popular drug
2 in the U.S., but is very expensive, and one with which
3 the National Health Service in the UK has been wrestling
4 over issues of access and how broadly should Receptin be
5 available.

6 The locus of innovation, this is something that
7 we'll talk about in particular in the next slide, and
8 that's just really geographically, where is the
9 innovation taking place, and to the extent it's
10 particular to a particular therapy type, what does that
11 mean for innovation?

12 We've heard a lot about cost structure. I won't
13 talk particularly about that, and then we'll return to a
14 patent issue.

15 In the interest of trying to convey something in
16 six minutes, there's really just three points that I
17 want to focus on. One is some determinants of
18 innovation. The second would be the effects of patents
19 on innovation, and we'll conclude with some comments on
20 consolidation activity.

21 We heard this morning that there was hand
22 ringing around 2002-2003 about the downturn of
23 pharmaceutical innovation at least as measured by
24 approvals from regulatory agencies.

25 This was a particular concern in Europe because

1 the problem was twofold for them: They not only saw the
2 same decrease in the approvals of new entities, but they
3 saw a continuation of the differential between the U.S.
4 and Europe. If you look back to the '80s, in the late
5 '80s and early '90s, most new products came from Europe,
6 and that is no longer the case, and so they retained CRA
7 to look and try to figure out both the determinants of
8 the particular downturn and what Europe might do to
9 correct what they see as an imbalance.

10 Not surprisingly, our first key finding -- I
11 should say as an economist, we put together a wonderful
12 proposal. We would have had access to unsurpassed
13 global data, and of course we didn't get it, so we don't
14 have the econometric study here, but our results were
15 largely based on qualitative interviews and were
16 generally consistent with those folks who did have
17 access to data that allowed them to do an econometric
18 analyses like Patricia Danzan, for example.

19 We found that there was no particular reason to
20 be overly concerned about a one or two year downturn in
21 the rate of approvals and in fact in the two years since
22 our report was published, those rates have picked up
23 again, and we also noticed what was commented on often
24 this morning about the in R&D productivity at least in
25 terms of measuring total spending against total

1 approvals.

2 We did note the geographic shift of
3 pharmaceutical innovation, and there's some interesting
4 reasons for this: Transfer pricing, tax incentives in
5 the U.S., the board place where folks who engage in the
6 vision like to live. These were all reasons cited by
7 folks who have moved to the U.S., but there are a couple
8 more that are particularly at issue for the biotech
9 industry, and that's, as I'm sure we can comment,
10 there's two big reasons you don't see more biotech
11 development in Europe and a third as well.

12 The first is that there's no European equivalent
13 of the NIH, so in some sense there's not much seed money
14 there to push along some initial innovation. There's
15 also, at least in comparison to the U.S., a nascent
16 venture capital network, and so we frequently hear from
17 manufacturers that there just isn't that funding that's
18 necessary to get the push over the initial hump. This
19 is why you see companies like Merck trying to develop
20 their own internal pool of venture capital to try to
21 stimulate local innovation.

22 So this leads I guess to the third point and the
23 Europeans are addressing this now. The third point when
24 we did the research was relative to the U.S., the
25 guidelines for the development of biotech drugs were

1 much more vague, much more difficult to follow in
2 comparison to what the FDA had, and that clarity allowed
3 a greater confidence in investments in U.S. operations.

4 So as a result at least, as far as the Europeans
5 were concerned, there was a much more stable investment
6 for traditional falls as opposed to biotechnology drugs.

7 Jumping quickly to the patent side of things.
8 What I want to make a quick point about is there are
9 really some after three, some after different types of
10 patent in a very broad sense that we've been dealing
11 with lately. I'm going to skip the first one, which is
12 what we most often think about is the patent that covers
13 the drug. That's the drug or molecule or perhaps the
14 process patent. Usually it's a combination of all those
15 things.

16 Manufacturers want to make sure that they cover
17 the waterfront, and they'll claim many, many different
18 things.

19 What's more interesting, and Dr. Berndt
20 mentioned this morning, is the increasing trend towards
21 theranostics. Receptin again here is a fabulous
22 example. Receptin is a highly effective breast cancer
23 drug for the roughly 25 percent of the women who over
24 express her too, so the instance question is: How does
25 Genentech structure it's clinical trials if it knows

1 upfront that the drug is going to be absolutely
2 worthless for some after three, some after quarters of
3 the potential sample population?

4 Do you develop a diagnostic on which to base
5 your innovation, knowing that subsequently reimbursement
6 will be limited to stuff a pool? Do you not, and
7 increase the innovation costs? Do you develop the test
8 yourself or do you partner with somebody?

9 The extent to which ownership is shared through
10 strict ownership through your licensing is going to
11 effect the efficiencies. If the test and the drug are
12 owned by different parties, neither has the incentive to
13 fully develop or the product or the diagnostic to its
14 economically efficient level.

15 And so we've got all sorts of interesting
16 strategic decisions going on in the consolidation or in
17 the development of biotech drugs. As far as I know,
18 there's only one manufacturer that had both -- that had
19 ownership rights not through licensing for both the
20 diagnostic and the product, and it took them so long to
21 develop the diagnostic that the patent on the drug had
22 expired by the time they had it, so not exactly the
23 strategy they had been pursuing.

24 The other interesting wrinkle here is that a lot
25 of these IP rights are far from determined, so some of

1 the most fundamental IP rights are still up for grabs.
2 These are the patents that came out of Harvard, out of
3 Yale and out of the University of California system that
4 covered the basic technology that is arguably the
5 foundation of the DNA sequencing. I say arguably
6 because nobody had any idea that the DNA sequencing
7 could take place when the initial licensing discussions
8 took place in the mid '90s and late '80s, and so now you
9 have substantial litigation that will determine who owns
10 the rate.

11 In the meantime Solara has decoded the genome.
12 They've sold their data. Arguably the outcome of that
13 litigation will result in a cascade effect as the
14 crowned winner of the IP looks for its stacked royalties
15 downstream.

16 I should say just out of fairness that the
17 business community has been sensitive to some of the
18 innovation issues that were raised earlier today, so in
19 terms of stacking patents, most licenses that you will
20 see say you're royalty rate is 10 percent if we're the
21 only person you have to pay, otherwise it's 5. There's
22 typically an adjustment for the field of use so if
23 you're a researcher you have much lower royalties than
24 someone who wants to commercialize, which of course
25 pinches if you have a researcher who has a glimmer in

1 your eye about becoming an entrepreneur.

2 Last point on devices, I'll skip through that
3 pretty quickly. This is just one more example of where
4 you're going to have the combination of both the therapy
5 and the diagnostic that either determines whether that's
6 an appropriate therapy for you or might be responsible
7 for actually getting the therapy into you.

8 Quickly on innovations -- sorry, merger effects.
9 Obviously this is all case specific. I'm obligated to
10 say that since the Federal Trade Commission and DOJ are
11 in the room. There's no global answers here, but
12 basically we think about mergers in two different ways.
13 One is -- the first way is an example of two companies
14 that both have strengths that are fairly similar, and
15 they merge because they've got complimentary research
16 portfolios or frankly because they have sales staff
17 trained who can go out and talk to the same doctors to
18 sell both kinds of therapies.

19 The other is when you get your mega mergers, big
20 companies with big portfolios that are really merging to
21 harness their expertise in the regulatory venues and in
22 sales and marketing, and it's that expertise which is
23 appealing now and why you see many more consolidation
24 efforts between big pharma and biotech, where biotech is
25 specializing in the development and the filling of

1 pipelines, and the traditional pharmaceuticals are
2 bringing to the table their sales and marketing and
3 regulatory expertise to get those products through the
4 end of the life cycle.

5 We can skip that. And just if you need to see a
6 data graph, I'll show you one we love because it
7 supports absolutely no one's position.

8 This was just an example that we came up with in
9 that innovation for the EU. Looking at the
10 GlaxcoSmithKline merger and categorizing sales by the
11 level of development, and some people look at this graph
12 and say Ah-ha.

13 Moving from here to here you don't really see
14 any big change, so it's not like we stifled competition
15 or we could look at this and say, sure, moving from here
16 to here or even going further, nothing really changes.
17 What did you accomplish that boosts innovation as a
18 result of the merger?

19 So with that, I leave you with those some after
20 three, some after thoughts and no real conclusions.

21 (Applause.)

22 MS. HOSKEN: Thank you, Peter. I think we can
23 maybe take one or two questions from the audience but we
24 will try to keep it brief so everyone can take another
25 break before the next session. Do I have questions for

1 the panelists, comments, thoughts? Everybody's tired.

2 MR. ADAMS: One of the things I was interested
3 in, Chris Adams, was are we really going to say or are
4 we seeing M&A activity as a driver for innovation? A
5 couple people mentioned IPOs are dropping off or IPOs
6 can't raise the funds, maybe somebody like Jim, do you
7 really look for M&As to be what your end goal is going
8 to be?

9 MR. BARRETT: The problem with that is when your
10 mother says you ought to get married. You have to find
11 a girl that's willing to take you, so you can't sort of
12 plan on a merger. You just don't know who will be
13 interested in what you're doing at what point.

14 I think the tone of the market suggests that
15 you're more willing to consider an M&A than you would
16 ordinarily. You would rather -- there is a liquidity
17 premium for being public that you get compared to
18 staying private, and so a punitive buyer would have to
19 meet that and exceed that premium if you're public as
20 compared to the circumstances when you're private, but
21 if the liquidity markets are despondent and you can't
22 get out, then M&A seems a much more increasingly
23 attractive outcome for you.

24 So I think it's in that context that you're M&A
25 versus going public sort of play out. If your liquidity

1 is strong you go out, and if liquidity is weak, the
2 merger becomes it increasingly attractive.

3 MS. HOSKEN: Maybe we should ask small biotech.

4 MR. QUIRK: The issue is that frequently small
5 biotech, particularly if you're a private company, you
6 have a gentleman like Jim on the board who are going to
7 be helping drive that decision, but at the end of the
8 day, if you're down to worrying about making payroll and
9 the equity markets aren't available to you, that's going
10 to happen, but people will do interesting things.

11 Like I said with Discovery Partners they kind of
12 said, we're going to sell off some assets and provide a
13 liquidity event by merging with this private company and
14 being able to take advantage of almost a new and
15 different portfolio. I think companies are being more
16 and more creative about that.

17 MS. HOSKEN: Do you see that sort of trending
18 over time where you feel like you need to sell in order
19 to go on?

20 MR. QUIRK: No. I think you need money in order
21 to go on, so how do you monetizes the assets, and maybe
22 it's granting rights to some of your crown jewels that
23 you weren't otherwise willing or things you wanted to
24 keep for yourself to sell for yourself, and you have to
25 make some decisions.

1 There are other way that are emerging in the
2 industry now with project finance. I think debt capital
3 is available to small companies in ways that hasn't been
4 available previously, so M&A is not necessarily the exit
5 strategy. It's got to make sense for everyone involved.

6 MS. HOSKEN: Any other questions? Why don't we
7 take a short break, and we can all come back in about
8 ten minutes for the next session. Thank you very much
9 to all the panelists.

10 (Applause.)

11 (A brief recess was taken.)

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1 PRESENTATIONS: ECONOMICS OF DTC ADVERTISING

2 CHAIR: MAUREEN OHLHAUSEN (FTC, OPP)

3 GINGER JIN (Maryland)

4 JAYANI JAYAWARDHANA (MUSC)

5 DAVID BRADFORD (MUSC)

6 JEFFREY YAU (FTC, BE)

7

8 MS. OHLHAUSEN: I'm Maurene Ohlhausen. I'm the
9 director of the office policy and planning here at the
10 Federal Trade Commission and our first presenter in this
11 panel is Ginger Jin, and she's an assistant professor of
12 economics at University of Maryland. To save time
13 everyone's bios are in the material so I won't recite
14 what you can read on your own, so thank you very much,
15 and we'll get started with Ginger.

16 MS. JIN: I would like to start with thanking
17 Chris and Maurene for including us in this wonderful
18 program, and this work is joined in with Pradeep
19 Chintagunta and Renna Jiang. This is quite preliminary
20 and ongoing work. I would say this is part of -- the
21 first part of a pretty big project in which we try to
22 understand how information flows in the life cycle of
23 prescription drugs, so by life cycle, we not only mean
24 the drug's itself approval or withdrawal, but also their
25 competitors and sort of introduction and outcome putting

1 drugs or withdraw of competing drugs.

2 So at this sort of the topic, we're going to
3 talks about Cox 2 inhibitors, which we all know is a
4 pretty traumatic class here, and the big drug Vioxx has
5 been withdrawn in September 2004 but to the extent that
6 we think withdrawal will have very interesting
7 implications and we think the learning that's going on
8 in aftermath of withdraw is very different from the
9 learning that's going on in the diffusion of those drugs
10 before withdrawal.

11 So in this paper our first attack will be on the
12 diffusion part. The data we're going to use is going to
13 be one year before the Vioxx withdrawal, so we're not
14 going to talk anything about withdrawals, but more the
15 introduction of any drugs or the usage of existing drugs
16 in our time frame so here we want to emphasize two
17 things in this learning.

18 The first thing is the learning based on patient
19 satisfaction when they consume a prescription drug, and
20 while focusing on that, we want to control for
21 manufacturing, advertising and other information, so let
22 me start with motivation of two major types of
23 uncertainties in prescription drugs. The first
24 uncertainty is -- there will be an average efficacy or
25 side effect that applies to every patient who use that

1 prescription drug, so that's sort of the average effect.

2 And then another uncertainty is about the
3 specific drug patient match so one drug that works for
4 patient one may not necessarily work for patient two, so
5 we have this average effect and heterogeneity. I think
6 the common wisdom is there will be absolutely truth and
7 also about the degree of heterogeneity about those drug
8 effects, but nobody know about those truths, so a lot of
9 institutions in this industry is trying to figure out
10 that information, if not all of the information, at
11 least part of that information.

12 So as the first gatekeeper, FDA requires
13 clinical trials before approval, but as Mark Duggan has
14 pointed out, those clinical trials are mostly short time
15 versus placebos and based and small sample size and so
16 forth, so there's more focus on average effect of the
17 drug instead of heterogenetic of the drug on specific
18 patients.

19 After approval, if I understand the law
20 correctly, there hasn't been a systematic study for post
21 approval surveillance, but in some cases, like in the
22 class work we're just going to talk about, there has
23 been clinical trials after approval. This most likely
24 will focus on a relatively longer term drug efficacy and
25 side effects, and based on those long-term clinical

1 trials and sometimes from patient feedbacks, these are
2 sort of educational report of mortality or various
3 significant side effects that FDA may have some updates
4 in terms of new labels or even withdrawals, but those
5 updates are quite discrete and infrequent.

6 A party that would have some advantageous
7 information in this whole business is drug
8 manufacturers, and they may get those information from
9 their process of developing the drug or the clinical
10 trials they conducted after marketing the drug or more
11 detailed patient feedback that goes to the manufacturer
12 but not goes to the FDA and so forth, but of course the
13 manufacturers sort of have an obvious incentive here by
14 not necessarily sharing every piece of that information
15 with the public.

16 They advertise heavily towards doctors and
17 consumers, but those advertising could be selected.
18 Information could be biased in the sense that it's
19 probably more -- focused on some aspects but not on the
20 other aspects.

21 So on top of all those, and we have seen drugs
22 that have been practiced daily in doctors's office so
23 the question we want to ask here is: How do physicians
24 resolve that kind of uncertainty in their daily
25 practice? Every day they probably get new information

1 about how their patient has taken the drugs and so
2 forth, and so how that information will effect the
3 doctor's practice in their future prescription.

4 So we're sort of thinking about two types of
5 learnings here, which will be associated with the two
6 types of uncertainties we just talked about. The one is
7 what I am going to call across patient learning, so this
8 is -- we believe there's overall quality issues that
9 applies to every patient. What you learn from one
10 patient should be applicable to another patient so this
11 is across patient learning.

12 The other learning is just specific to this
13 patient. We see some side effects happen on this
14 patient. This will help the doctor to update I believe
15 how this drug works, how this drug works on that
16 specific patient and with that specific drug, and that
17 will be learning within that patient and within that
18 drug.

19 So we view our contribution will be to be the
20 first study that systematically combines the two types
21 of learning in one model. In previous literatures we
22 have seen papers focus on across patient learning or
23 within patient learning, and in both types of studies,
24 they basically are using the diffusion pattern of drugs
25 or the prescription pattern of individual level of data

1 try to infer what kind of information the doctor must
2 have when they have that kind of evolution of drug
3 usage.

4 Undermining that is just saying there will be
5 information that, but we just don't know what it is. We
6 just infer from the prescription pattern. What's unique
7 in our study is that we actually ends up with a pretty
8 unique data that will allow us to observe how patient is
9 satisfied or dissatisfied with a drug after they consume
10 it, so to that extent we'll be able to tell how much of
11 the prescription and how much of the changes in
12 prescription pattern is because of the changes in
13 patient satisfaction rather than just infer it by a
14 functional form and so forth.

15 So in doing so we need to control for a lot of
16 other sources of information and like direct to consumer
17 advertising and direct to doctor advertising, and as
18 Marta Wosinska suggested, that we should control for the
19 news coverage and probably professional articles about
20 those drug efficacy over time, and at this stage, we
21 have cluttered the news and article data about haven't
22 been able to incorporate those into the whole structure
23 model so I'm not going to present the results today.

24 Okay. So to be more detailed about data, this
25 data is selected by a marketing and research company

1 called IPSOS. What they do is track a national
2 representative sample of I think about 16,000 drug
3 patients so they ask every patient to take a diary of
4 what drug they take each day and what's the dosage and
5 so forth.

6 Starting in 2001 they also asked five questions
7 of how the patients feel about the drug after they are
8 taking it, so this could be do they think the drug is
9 effective or not, do they think the side effects is
10 important or not and how quickly the drug would take the
11 effect in their body and is it easy to take and so forth
12 like that, so there together is five questions. So
13 basically our research will be focused on those five
14 satisfaction measures while controlling for advertising
15 intensity.

16 So I guess with this crowd, I don't need to talk
17 too much about how important this class is here. This
18 is a very traumatic cost. Cox 2 inhibitors were
19 basically introduced in January of 1999, and this is
20 sort of as an imperfect substitute to the traditional NC
21 ad as pain relievers, and traditional NC ad, I think in
22 medical terms, they inhibit both Cox 1 and Cox 2, so
23 it's well understood that the traditional NC ad has GI
24 risk for patients.

25 Clinical trials has shown some evidence that Cox

1 2 inhibitors may have some potential to reduce the GI
2 risk, so when Celebrex was first introduced, it was
3 heavily advertised so-called safer alternative to the
4 existing painkillers so that -- the market picked up
5 quickly by September 2004, which is right before the
6 withdrawal of Vioxx. We have about ten million patients
7 taking any prescription drug in Cox 2 inhibitors. The
8 annual sales is as large as \$6 billion and advertising
9 dollars spending on this class is as high as 400
10 million. I think Vioxx is actually the most advertised
11 drugs toward consumer in its launching year in 2000.

12 So this is sort of very heavily advertiser
13 costs, but after a long time clinical trial showing that
14 Vioxx has increased the cardio risk by about double
15 compared to a placebo, then Merck has decided to
16 withdraw Vioxx in September of 2004, and shortly after
17 that, more clinical trials was showing that the sir
18 drug, Bextra, which was introduced in 2001, has similar
19 CV risk and also has some skin irritations so it was
20 pulled out of the market in April 2005.

21 So just in less than six years we have seen
22 three drugs but two has been pulled out of the market
23 and as of today only Celebrex is still marketed in
24 doctor's office, okay.

25 So this picture is showing you basically the

1 number of new prescriptions in Cox 2 from 1999 to 2003,
2 so you can see will dark blue represents Celebrex which
3 is the first drug. It was sort of picking up the market
4 almost immediately after its introduction, and it's
5 pretty stable afterwards.

6 And then Vioxx was introduced only five months
7 later. It's sort of slow in the beginning but it pick
8 up in about a year, about the same market share level
9 with Celebrex. Then when Bextra was introduced in 2001,
10 it starts to get market share but it never reached the
11 same level as Celebrex and Vioxx.

12 And in terms of the overall prescriptions for
13 all those three, Cox 2s, you can see after 2000 and
14 after 2001 the overall number of prescriptions consuming
15 any Cox 2 is sort of stable over time, so you can see
16 the introduction of Bextra is mostly kind of a market
17 stilling effect from existing Cox 2s instead of
18 expanding to a new number of prescriptions.

19 This is a trend detailing expenditure in the
20 same time frame. I think what we take away from this
21 picture is that almost every drug here is spending about
22 the same amount of dollars and behaving no matter how
23 old or how new those drugs are, but the direct to
24 consumer advertising is a little bit different picture.

25 Basically there's no direct to consumer

1 advertising for Bextra at all, and Vioxx was very
2 heavily advertised at the beginning, but then it sort of
3 goes down a little bit. Overall Celebrex and Vioxx has
4 fluctuated a lot over months, two months, and I will
5 be -- we don't know why Bextra was not advertised at all
6 in direct to consumer channels.

7 One speculation is it's because both Celebrex
8 and Bextra were owned by Pfizer, so Pfizer may decide to
9 market one drug while not marketing the other drug too
10 much, but I would like to hear more about that from Dr.
11 Manning, whether that's speculation is right or not.

12 So this is the summary of satisfaction data we
13 have from our individual patient data, so here the scale
14 is one means extremely satisfied and five means
15 extremely dissatisfied, and this is average of all the
16 five measures we have on their satisfaction, so you can
17 see if you just look at the last row of -- just look at
18 the last row of the numbers. You can see Vioxx actually
19 was rated the highest amount of three drugs, although
20 the margin between Celebrex and Vioxx was very close,
21 and they would be statistically very significant.

22 And Bextra is slightly lower than both of them
23 in terms of the satisfaction matrix, so this is sort of
24 corresponding to the FDA decision that Bextra has more
25 side effects is not only in the CV risk but also in some

1 skin irritations.

2 If you look at the picture, the bar picture
3 below it, you can see that's the satisfaction number,
4 also more dispersed for Bextra because Bextra is a newer
5 drug as compared to the other two.

6 So the first question we would like to ask is:
7 Are there any evidence of learning in this data? So we
8 just do a very rough cut of the data to see what kind of
9 patients has switched on those brands, so we can see the
10 average switching rate is about 8 to 10 percent with the
11 lowest in Celebrex and highest at Bextra, and if we run
12 the regress question of -- if we run a rough regression
13 of whether a patient has switched prescription based on
14 how satisfied the drug efficacy or side effects has been
15 and we find that the side effects are easy to take, has
16 no affect on the drug switching probability, but the
17 satisfaction of drug efficacy does have a significant
18 and positive effect on this.

19 We also regress number of new patients, patient
20 satisfaction. This is sort of like pulling everyone
21 together, and this is confirming our understanding that
22 more satisfied patient seems to relate to more number of
23 new patients while detailing and other advertising does
24 not have a -- have a big impact in this regression other
25 than the drug.

1 The only thing that shows up, the only
2 advertising that shows up significant here is direct to
3 consumer advertising, which we don't understand, but we
4 -- sort of like similar to it's kind of confirming our
5 prior, but we don't understand why direct to consumer
6 pick up but detaining does not.

7 So that's sort of like the reduced form rough
8 cut of the data, and while we're heading now into the
9 structural model, given that we don't have much time
10 here, I'm going to skip most of the assumptions I have
11 on this, so basically I'm presented you a very
12 preliminarily version of our structural model.

13 And in this model we're thinking the physicians
14 are doing phasing, updating in their learning process,
15 so when they receive patients signals, they try to
16 integrate them in the basian and then update their
17 belief into a posterior your and that posterior would
18 guide their new prescription decisions.

19 One caveat of our data is we actually don't have
20 doctor ID, although we can track patients over time
21 quite well, so one assumption we have here is we presume
22 doctors share their patient experience within the
23 geographic area and here is by a region. We can
24 carefully test that assumption.

25 So I'm going to skip the model. It's basically

1 just a utility based choice model of drugs, and while
2 the utility is depending on doctor's posterior belief
3 about this drug, which posterior will be formed based on
4 the former experience the doctor would gain from other
5 patients or same patients, so with all the mathematical
6 formulas and try to match this model with the data we
7 observed to see whether the switching patterns we have
8 or more generally the prescription patterns we have
9 there will match the model we have in mind.

10 Okay. So I'm going to accept this. Let me just
11 jump into the main results we have here. The main
12 results here, I'm showing you three columns. The first
13 column should be taken as the main results where we're
14 assuming risk neutral, and we allow both type of
15 learning going on.

16 In the second column is the same risk preference
17 but we only allow across patient learning. In the third
18 column we focused on within patient learning but do not
19 allow cross patient learning so you can see the first
20 one embedded in the other two.

21 So the first message I would like you to take
22 from this is if you look at the overall fit of those
23 three models, you can see the model that increased both
24 types of learnings has explained the data better than
25 the other two. If it's compared to relative magnitude

1 of the fit of the data, it seems like majority of the
2 variation captured in the model coming from within
3 patient learning rather than across patient learning, so
4 that's kind of that's saying if doctors are learning
5 about there, they most likely are learning about how a
6 drug fit a specific patients instead of learning about
7 overall quality about that product, and coefficient you
8 want to look go is this one, this basically is a
9 coefficient and it turns out to be significant and
10 positive and this basically means how important if the
11 doctor is saying the signals they got from patient
12 experience is, okay.

13 Then we can estimate the prior, the doctors have
14 about the average effects of those drugs, and those
15 priors are compared with sort of how noisy the signal
16 is. You can see the priors has much smaller variances
17 as compared to the variance of the noise which means
18 that the doctors actually start with a very tight prior
19 about average effect, and if they're updating that prior
20 it will be very slowly updating, okay.

21 So that means the cross patient learning will be
22 very slow given that they have a pretty tight prior and
23 given the noise is relatively more dispersed than their
24 prior.

25 But if you look at the priors on the specific

1 patient drug match which is pretty -- which is here,
2 it's I would imagine pretty similar to the variance we
3 have on the initial noise, so that means the specific
4 patient and drug match is much more dispersed and
5 doctors can learn relatively quickly those things, okay,
6 so that's why in our data you can see within patient
7 learning seems more important than cross patient
8 learning exactly because it's driven these kind of
9 priors.

10 Let me say the last thing about the advertising
11 coefficient that we have in this model. We were
12 thinking of advertising as controls that may capture
13 something else going on in this market, but the bottom
14 line is that we don't see much significance and positive
15 effect from those advertising.

16 Actually in our preferred model we see the
17 detailing has a positive but a lousy effect on the
18 choice while the direct to consumer advertising even
19 have a negative effect, so this is kind of a puzzle to
20 us, and we're working more to see whether this actually
21 reflects some news and medical articles effect which
22 could be correlated with those advertising.

23 So jump to the main conclusion. Basically from
24 this very preliminary result, we think we learned
25 several things. The first is we think patient learning

1 plays a much more important role in drug diffusion than
2 advertising while pending on those will survive our
3 robust tasks.

4 And the second result is we find that doctors
5 held a very strong prior belief about the relative
6 efficacy of those three drugs, and because patient
7 satisfaction signal is how much noisier than the priors,
8 so doctors learn about patient satisfaction information
9 in terms of across patient learning is pretty gradual.

10 In comparison, we find that none of the
11 advertising variables have significant and positive
12 impact on prescription choice in our time period, so it
13 seems like there's something learning going on but it's
14 not necessarily related to advertising.

15 We are doing a lot of ongoing work here. Some I
16 already mentioned that we're going to incorporate news
17 and articles in this framework. We're actually planning
18 to NC ad is as to outside good because that could be an
19 important choice decision in this whole framework. We
20 also are trying to distinguish time dependent learning
21 from all observed heterogeneity.

22 So that's the main thing we're going on in terms
23 of robustness check, and I will stop here, and I look
24 forward to hearing your comments thank you.

25 (Applause.)

1 MS. HOSKEN: Does anyone have any questions at
2 this point? Do we have another microphone? Over here a
3 question.

4 (Discussion off the record.)

5 MS. JAYAWARDHANA: So I'm Jayania Jaywardhana
6 from University of South Carolina. I'm discussing the
7 paper that Ginger just presented, which is looking at
8 patient learning and advertising, how it affects on
9 prescription behavior. So the object of the paper as
10 she just mentioned is to describe how patient
11 satisfaction and drug advertising affect the diffusion
12 of Cox 2 inhibitors.

13 And she is still working on actually estimating
14 the full model with the risk neutral model, but for now
15 she's viewing the results of where the discover pyramid
16 is zero. The risk neutral model results, and these
17 results are both learning across patients and learning
18 within patients play an important role in explaining
19 drug diffusion within this class, and advertising has
20 little or no impact on explaining drug diffusion.

21 I like the approach that they have taken here.
22 They're using basically learning approach to explain how
23 a patient learning effects prescription behavior, and
24 also I like the fact that the model both across patient
25 learning and within patient learning, and they do have

1 an access to a unique data set where they get the
2 patient level satisfactory which actually allows them to
3 identify these to offer separately.

4 Moving on to more comments and questions. The
5 model that we presented does not capture the information
6 effects of advertising, and personally I think
7 information effects of advertising could have an impact
8 on patient learning, and I think if you can incorporate
9 this informational advertising effect into the model,
10 that would be much more interesting.

11 And the model that you're presenting has
12 advertising entered into the analytic function directly.
13 However, in the paper it says this specification doesn't
14 necessarily imply persuasive advertising. According to
15 advertising, however -- we all know this advertising and
16 analytic function basically captures the first effect of
17 advertising, so I don't know. I think if you can
18 clarify that sort of in the writing, that will be
19 helpful for the reader.

20 And also the assumption which is more of a
21 question that you made that doctor's prior belief on the
22 distribution of patient heterogenous is the same as the
23 actual distribution, I wasn't quite sure what the
24 feeling behind this assumption was and if you can
25 provide an explanation for the reader, that would be

1 very helpful.

2 Moving on to identification and estimation, in
3 identifying did the risk pyramid, you mentioned you
4 would have to make functional form restrictions, but
5 don't specify what exactly this functional form
6 restrictions are in the paper, so for the reader it's a
7 little bit difficult to find out what they are exactly,
8 and if you can specify that, it would be good, and also
9 I was wondering whether it's more of a pyramid
10 restriction other than the a functional form
11 restriction.

12 And the results that you're presenting as I
13 said earlier is a risk neutral model when the
14 restriction pyramid is zero, but one you're writing down
15 the original model, you mention or specify this risk
16 pyramid to be getting than zero so it seemed to me it
17 could have been very good if you estimate the model
18 income as one instead of zero, and I think the results
19 would have been much more credible also if you estimate
20 when gamma is one instead zero and basically you're
21 being consistent then with your model specifications or
22 the pyramid specification in the model here.

23 Finally patient learning data could be
24 correlated with advertising data, and I was wondering
25 whether this introduces a bias, and I wasn't quite sure,

1 so that's more of a question that I have for you?

2 So those are the only comments I have, and I
3 hope these will be helpful and I'm looking forward to
4 reading the -- seeing the results of the full model.
5 Thank. (Applause).

6 MS. OHLHAUSEN: Chris, do we have time for
7 questions or should we move on to the next one? I'm
8 sure the panelists would like to talk to the people
9 afterwards or you can contact them by Email.

10 The next presentation is by David Bradford who
11 is a professor in the Department of Health,
12 Administration and Policy and director of the Center For
13 Health Economic and Policy Studies of the Medical
14 University of South Carolina.

15 MR. BRADFORD: Quite a mouthful.

16 MS. OHLHAUSEN: Yes, that's the longest
17 introduction thus far.

18 MR. BRADFORD: I've been watching everybody play
19 with this microphone wondering when it's going to break
20 out in song. It seems like I'm singing Valerio or
21 something when you were standing up here with this.

22 Again I want, as with the other presenters
23 thank, thank the FTC and Chris Adams for putting this
24 together. This has been a very interesting day, and I
25 think it's been a testimony to how vital and diverse

1 this field is in that you see papers on -- nearly each
2 paper's sort of provides distinct areas of analysis, so
3 I learned a lot this morning, not the least of which
4 that you can press F 5 to make a PowerPoint presentation
5 start, so it's been a great day all around.

6 So I would like in the 20 minutes that I have to
7 go over a project that is part of the larger initiative
8 that we're undertaking in MUSC, and I do want to
9 acknowledge and thank the support of AHRQ and the
10 National Heart, Lung and Blood Institute for this work.
11 We're looking at a range of issues in direct consumer
12 advertising, and that's what I'm going to focus my
13 discussion on here this afternoon. Today I'm going to
14 be talking about cholesterol treatment, though I'll
15 mention some of the other research results that we had.

16 As just a very brief background, as probably all
17 of you know, the United States is one of the few
18 countries along with New Zealand to allow relatively
19 unrestricted direct consumer broadcast advertising for
20 prescription drugs. Prior to August of 1997, broadcast
21 ads were technically legal and in fact were common.

22 I remember the first one that I have direct
23 memory of would have been in the very early 1990s when
24 Claritin was advertising on television, and at the time
25 there was a restriction in place that these ads could

1 either mention the name of the drug or it could mention
2 the condition for which the drug was effective but not
3 both, and so Claritin for example said, Claritin, a new
4 day dawns, ask your doctor if Claritin is right for you,
5 and you saw an attractive woman in profile smiling in a
6 green field, and it left lots of questions in my mind at
7 least as to what the effect of the drugs would have
8 been, was it an antidepressant, antihistamine or
9 something to improvement your looks, which would have
10 been attractive and useful for me from time to time.

11 After August of 1997 the FDA permitted drug
12 manufacturers to advertise in broadcast media by
13 announcing the name of the drug and what the drug would
14 treat as long as they referred patients to some other
15 source for the package insert information.

16 Now, this created a great deal of controversy,
17 and kind of keeping with the issue of direct to consumer
18 advertisement in the forefront of policy makers and to
19 some degree researchers's minds ever since. I do want
20 to point out that it sometimes is suggested to that
21 policy shift was the triggering factor to the growth in
22 DTC, and this is not anything new, but many people have
23 acknowledged that really in August of 1997, we had
24 already begin to see the growth in DTC before that
25 point. This was a phenomena that's been going on for

1 quite some time.

2 We're not here today or at least I'm not here
3 today to talk about testing whether this policy shift
4 had a major impact. We're going to be taking a much
5 more micro oriented look at things. In particular what
6 we're going to try to do is to see whether or not DTC or
7 DCA as I have it here, I should say, direct consumer
8 advertising has any effect on three components of
9 physician welfare.

10 And that is does it increase the likelihood the
11 patient is compliant with the prescriptions they're
12 given? Does it help increase the likelihood that
13 therapies are successful? And I'll explain to you in a
14 minute why we suspected that might be the case, and also
15 to see whether or not DTC affects different kinds of
16 patients in different ways, in particularly is going to
17 impact patients who have greater clinical need more or
18 less strongly than patients with less clinical need.

19 To do this, in this particular case, we're going
20 to looking at a class of drugs, statin drugs, that are
21 useful for coaling hyperlipidemia or high cholesterol.
22 I do want to mention at the outset in case I forget in
23 the press of time to mention later, our measure direct
24 consumer advertising is going to be advertising for
25 these three brand name drugs.

1 The measure of prescribing and adherence is
2 going to be any lipid lowering drugs, largely in our
3 samples statin drugs, but there are a few other lipid
4 lowering such as Niacin that will be included as well,
5 so we're looking at statin advertising on anti lipid
6 medications here.

7 Now, very, very briefly I want to discuss some
8 of the literature. A number of people in the room -- in
9 fact I think nearly every bullet here has someone in the
10 room represented who has been on these papers, so the
11 room is well informed about this, but in any event
12 Ginger and her colleague have done several papers on
13 DTC, and with regard to overall prescribing using data
14 from the National Ambulatory Medical Care Survey, they
15 find that physician visits have increased during months
16 of higher spending, although the spending itself didn't
17 seem to change prescribing patterns.

18 Meredith Rosenthal, and I believe Ernie was on
19 this paper as well, did some work looking at DTC on a
20 variety, a whole host of different drug classes intended
21 to find that there were sort of class level effects but
22 again brand effects weren't largely unaffected, and
23 Marta Wosinska who you will hear in a minute, has also
24 done work on looking at DTC on prescribing and found
25 some relatively small effects but effects that dependent

1 on formulary status.

2 With regard to adherence again Julie Donahue and
3 her coauthors have found some adherence affect, and
4 Marta in a different study as well found small class
5 level adherence of effects so we have reason from the
6 literature to think that adherence might be something
7 that is impacted by DTC as well as sort of the general
8 prescribing that perhaps the manufacturer might care
9 about, although clearly adherence is an issue for them
10 as well.

11 I want to mention two other studies that have
12 come out of the sorter broader projects that we have
13 going on down at MUSC because they're going to be
14 important for motivating why we're doing what we're
15 doing.

16 The first of these is a study that just appeared
17 in Health Affairs that looked at sort of physician
18 level, physician practice level effects of DTC on
19 whether or not you got an increase in visits of patients
20 with osteoarthritis who were taking Cox 2 inhibitors for
21 the treatment, daily therapy for Cox 2 inhibitors,
22 whether or not that prompted increased visits and
23 increased prescribing.

24 What we tended to find was in fact visits did
25 respond to DTC but we largely found class effects with

1 regard to prescribing patterns, that Vioxx in
2 particular, the advertising for Vioxx is effective at
3 prompting not only its prescribing but prescribing for
4 Celebrex as well. Ad spending for Celebrex at least in
5 our data was not as effective as stimulating that, I'm
6 sorry to say.

7 In another study and one that's going to also
8 motivate what we're doing, and I should say the study
9 that unfortunately appeared in the schedule today, so
10 you're not hearing a study on the impact of timing of
11 treatment, but that study did look at whether DTC had an
12 impact on how long people waited in between the time
13 they were diagnosed with osteoarthritis and when they
14 began daily therapy with Cox 2 inhibitors.

15 The interesting thing about that for us was we
16 were able to classify patients into people that were
17 good candidates for therapy and bad candidates for
18 therapy, in essence people who had had prior
19 prescriptions for H 2 antagonists and other gastro
20 protecting agencies would have been the ones most likely
21 to benefit from the gastro protective components of the
22 Cox 2 inhibitors, and after August of 2001 with the
23 publication of an article by TaPaul and some colleagues
24 that pointed out the cardiovascular associated with
25 Vioxx, people who had cardiovascular comorbidities would

1 have been bad candidates for the Cox 2 inhibitors,
2 particularly Vioxx, and should wait longer.

3 And what we found was that DTC in fact pushed
4 people in exactly this way, that when people were
5 exposed to more DTC, they tended to adopt quicker when
6 they this these gastrointestinal morbidities, and after
7 August 2001, people who had cardiovascular morbidities
8 and who were exposed to more DTC in fact waited longer
9 so DTC seemed to have an effect. It's consistent with
10 and it's hard to think of an alternative explanation
11 except that there's information in these ads that's
12 improving the matching of patients in some way, and
13 we're going to try to explore that component in a more
14 indirect way at least here today.

15 So the rationale for the paper that we're
16 talking about at this point, given the research we have
17 on Cox 2s and others have done as well, we seem to find
18 that Cox 2s are supportive that -- the DTC research is
19 supportive of the ideas that it's encouraging patients
20 to consult physicians as Paul Rubin and Alison Keith
21 have proposed more than a decade ago, and it also seemed
22 to assisting patients and physicians in matching
23 therapies better.

24 Now, if both of those things that are true, then
25 the work that we're going to be doing right now in

1 statin therapy, we should see that greater exposure to
2 the direct consumer advertising should improve adherence
3 to lipid lowering therapies and if it improves matching,
4 then there's, some reason to suspect that even
5 independently of the adherence effect, we might see an
6 improvement in clinical outcomes, and I'll talk a bit
7 more about what clinical outcomes we mean.

8 So we're going to do this by looking at a set of
9 patients 51,000 patients who have already chosen to
10 adopt therapy and see how well they adhere to it and
11 what their clinical LDL outcomes are, so we're going to
12 basically break it down into patients who initiate
13 therapy during periods of high exposure to DTC versus
14 low exposure to DTC. Instead of having a continuous
15 measure, we're going to adopt or modify the approach
16 that Julie Donahue and her coauthors took in that
17 regard.

18 Now, what's this data source that we have.
19 We've actually collaborated with a research network that
20 consists at least at this point in time actually now of
21 135 primary care practices scattered in 35 different
22 states. You have see the states listed in the practices
23 listed with the stars there. Overall we actually have
24 about 300,000 patients over this six year time period
25 who have had some lipid contacts, whether it's a lipid

1 lab or a diagnosis for hyperlipidemia or a prescription
2 for statin.

3 We have just now completed -- my colleagues,
4 Jeff McCulla and Jayani who you just heard from a minute
5 ago just completed construction a monthly panel. We
6 have about 10 million patient month observations we can
7 try people for a long time, but what we're going to do
8 today is look at actually the 51,000 or so who adopted
9 therapy on the 106 practices that we had before a few
10 weeks ago where the work was completed and we're going
11 to see how their exposure to DTC affects the likelihood
12 that they adhere to therapy for six months and their
13 clinical outcome.

14 So we're actually interested and excited about
15 this data. In some sense it's large. We have a huge
16 data set we can follow individuals for six years, and
17 we're able to then match them to local and national DTC.
18 Local DTC is matched by putting them to their nearest
19 media market we have in our data, and we can also
20 exclude people who are more than 100 linear miles away
21 from a media market we want. It turns out that doesn't
22 seem to matter for us.

23 Let me tell you a little bit, very briefly about
24 how we're going to measure the clinical outcome. This
25 is a point where as an economist in a medical school I

1 give the caveat that I'm not a physician. I don't play
2 a doctor on television and I have never stayed at a
3 Holiday Inn Express.

4 However, I am in a medical school and so I have
5 a lot of doctors around me, which means I'm competent if
6 you have questions to forward your questions to them,
7 and they can get back you to with the answers about
8 them.

9 But the clinical collaborators we have helped us
10 refine the measure of how we're going to think about
11 clinical outcomes, and of course as you probably know,
12 the main clinical outcome with regard to elevated lipids
13 is the control of low density lipoprotein or LDL which
14 is a fat like substance that is in the blood stream, and
15 there are a number of primarily pharmaceutical
16 interventions that are effective at reducing LDL levels.

17 Life-style modifications are obviously by
18 guideline the first line approach. Lifestyle
19 modifications have not been found to be highly
20 effective. Statins and other drug therapies however are
21 effective.

22 So we have two dependent variables that we're in
23 essence going to be examining here today. The first one
24 is going to be the easiest one to talk about, and that
25 simply is: Are people on therapy for an extended period

1 of time?

2 Now, as I've just said, we have just finished
3 our full panel so we'll do the study of long term
4 adherence later. Right now we're looking at a study of
5 short term adherence, so we can observe when a person is
6 first prescribed a prescription for an anti lipid drug.
7 We can see how many daily doses there are in the initial
8 prescription, how many refills there are and when the
9 person renews this prescription, and so we can in
10 essence construct a treatment spell from that, and again
11 working with our clinical colleagues, allowing for
12 people missing days occasionally, a treatment spell in
13 essence ends when we have been 90 days without any live
14 doses that the person ought to have for them.

15 So we're going to define in this study a simple
16 dichotomist variable for one of the dependent variables
17 and have you adhere to your therapy for at least six
18 months, and there's a surprising number of people who
19 don't in fact adhere for that length of time.

20 Now, the outcome measure is going to be a little
21 more complicated than that. One could of course look
22 simply at the level of LDL in the bloodstream, and this
23 graph shows you the pretreatment LDL levels on average
24 in our population and the post treatment LDL levels,
25 which are falling with time, not clearly as a

1 consequence of DTC, although of course we would like to
2 know if DTC is a factor, but it's not going to be
3 appropriate for us to simply model what is the -- even
4 the chain in LDL and actually get a necessarily
5 clinically relevant measure.

6 The reason for that is physicians titrate the
7 dosage of these statin drugs in order to achieve certain
8 goals. The one picture that I have of a book up there
9 was the cover of the Adult Treatment Panel III report
10 that NHLBI produces generates clinical guidelines for
11 the treatment of hyperlipidemia, and it actually
12 establishes LDL threshold before you begin treatment and
13 thresholds to which you're trying to get people's LDL
14 levels to.

15 The difficulty is if we just use the raw number,
16 the raw LDL levels, we're going to miss the clinical
17 behavior which is trying to get people to a different
18 point, so two people who might have -- let's say we have
19 two people each with a goal of 100 milligrams per
20 deciliter of LDL in their bloodstream, if one starts
21 with an LDL level of 120, they of course will receive
22 therapy and titrate it down until they get their LDLs to
23 one hundred and then of course you would stop titrating.

24 A person who has an LDL of 200 will need to drop
25 their measure by a hundred points in order to get to

1 that same goal, and then you would stop titrating. The
2 difference is or the point is that both have achieved
3 the goal that they set out with their physician to
4 achieve, one by doing a 20 point drop and one by doing a
5 hundred point drop.

6 We're going to avoid this by simply saying what
7 are the LDL goals individuals have and have they been
8 able to obtain them by six months? The glory of the
9 data we have which is electronic medical record data
10 like chart abstract is we basically observe all the
11 information we need with a few exceptions, to classify
12 what the LDL goals ought to be for each person in our
13 sample, and that depends upon whether they have
14 hypertension or low levels of HDL, which is actually a
15 protectant. Higher HDL is a protective factor for
16 developing atherosclerosis, age and other diagnoses, and
17 we can then classify people based upon what their LDL
18 goals are and then see whether or not after six months
19 they've attained them.

20 So our second dependent variable is going to:
21 Be have you obtained the LDL goal? Now, this is of
22 course a fraction of the population, the blue line, who
23 did achieve the LDL goal matched with the DTC spending
24 for I believe this is the -- actually the national
25 spending, not the local but just the national spending.

1 The point of that slide is you can't tell anything.

2 The next approach of course is sort of maybe
3 where we would stop if I were -- if this was a clinical
4 audience, not to disparage clinical audiences, but a
5 simple breakdown of what the rates of attainment are
6 across the different treatment goals, and basically we
7 see that if you're in high DCA when you start versus a
8 low DCA month, ignoring the people in the middle, high
9 exposures associated with greater levels of goal
10 attainment across the board, stronger measures in the
11 most clinically stringent group than in the least
12 clinically stringent group.

13 But again this is only sort of dichotomist
14 comparisons and really ignores an awful lot of the
15 work -- an awful lot of interesting effects and also
16 coverts, so what we're going to do is we're going to
17 estimate a simple model, a bivariate probit which we
18 have joint distribution and the likelihood that you
19 adhere for six months and the likelihood that you attain
20 your goal after six months.

21 The only point of this last little bit is to
22 note that if went to know the marginal effects, it of
23 course depends upon modeling the joint probability of
24 adherence and attainment, so I'll show you those
25 marginal effects in a couple minutes I'm thinking now.

1 So our advertising measure as I mentioned at the
2 beginning are the spending for Lipitor, Prevacol and
3 Zocor in any month, but again we're looking at statin
4 therapy or any lipid therapy, overwhelmingly statin, and
5 we're going to discotomize this into, did you begin your
6 therapy after exposure to a high dose of -- if you want
7 to think of it in those terms, of DTC just before you
8 began your statin therapy or not, and the high doses
9 being in the upper 25th percentile.

10 We also control for the usual suspects as far as
11 clinical and individual indicators are, and we have a
12 physician fixed effects in one set of the models and not
13 in the other. They're all focused on the physician
14 fixed effects.

15 Now, here are the raw parameter estimates from
16 our bivariate probit models, and what I want to point
17 out here is we see basically that DTC -- being in a high
18 DTC month has across the board strongly significant
19 impacts on the likelihood that a patient adheres. These
20 are T stats in parentheses, and in this case 5 percent
21 is the 5 percent that we're looking at because we have a
22 lot of observations, so we don't want to go to the 10
23 percent levels so you're looking for something in the
24 1.8 or higher range.

25 As far as independent effects on attaining the

1 LDL goals, we actually for the LDL of 100 group find
2 that national advertising matters, and that in essence
3 both matters for the intermediate group and nothing
4 independently for the least restrictive clinical group.
5 They're not responding in terms of achieving their goals
6 as much as the other two groups are.

7 Now, the marginal effects and the punchline here
8 that I will end with in just a second is to note that
9 when you model jointly the probability that you both
10 adhere to the goal and adhere to your therapy and
11 achieve your goal, we're basically getting significant
12 positive effects from having great exposure to DTC which
13 ranges from about a 3 percent to about an 8 percent
14 increase in the likelihood of those two events happening
15 at once.

16 And I will say also from a clinical standpoint
17 3 to 6 percent improvement in an outcome is not trivial.
18 It's actually larger than you get in many other sort of
19 population based measures of intervention, so it's a
20 pretty different size affect.

21 So in conclusion coronary heart disease is a
22 major source of morbidity and mortality in the United
23 States. Statins have a large relative improvement in
24 relative risk of coronary mortality, and so if DCA is
25 something that can help improved matching, there may be

1 significant welfare effects to patients, and we
2 basically find it's the case, that high local and
3 national advertising increases adherence pretty much
4 across the board, that high national advertising and
5 local advertising improves achievement independently for
6 certain groups, and overall we're getting about a 3 to 7
7 percent increase in the joint adherence and attainment
8 and goal attainment for these patients.

9 So our take home message of this is that
10 consistent with the other work we have had, there does
11 seem to be positive welfare effects that are coming from
12 this DTC and we're not in the camp that's encouraging
13 strong re-regulation of this, at least until more
14 studies like this have been funded for folks like me,
15 and we have time to do them.

16 So thank you very much.

17 (Applause.)

18 MS. OHLHAUSEN: Thank you. The discussion on
19 Dr. Bradford's paper is Jeffrey Yau from the FTC's
20 Bureau of Economics.

21 MR. YAU: Thanks. I'll bring up my slides. I
22 thought that I did it last night. I run everything and
23 I produced this tables. Okay. I have it.

24 I want to thank David for presenting the paper,
25 and the paper is very interesting, makes very

1 interesting reading and -- nothing that I have not
2 thought about before, and I would like to focus a lot
3 more on the scope of the paper because as you've seen
4 the data set is great, and you'll hear me say a lot on
5 data set later, so I don't want to say you could do this
6 or do that as well. I just want to focus on the scope
7 of the paper.

8 So the objective of the paper is to estimate the
9 average impact of the DTC on two things: One is on
10 adherence to the therapy, and the other one is the
11 success of achieving a particular level of the target
12 level using the unique data sets.

13 Let me phrase this question, which is: In other
14 words, what we would like to know is what would have
15 happened to the patients' adherence to the statin
16 treatment and the success of achieving the target LDL
17 level had they not been exposed to the heavy DTC
18 markets? So I think they mentioned something about a
19 heavy DTC market, but I just use this terminology here
20 by really being exposed to a market that is heavy DTC or
21 like DTC.

22 So the overview, this I think is heading in the
23 very right direction because we do like to know in this
24 literature the effect of the DTC on the patient's level
25 using the patient's level data set, and as David pointed

1 out in his paper, this is one of the very few papers
2 that looked into this directions.

3 Great data set. I don't want to repeat how
4 great this data is, and in fact, after I read this
5 paper, when I talked to him, David said right now it's
6 much better than what was used to estimate for this
7 particular paper that I read.

8 One thing I do like a lot about the paper is
9 that they point out very carefully several important
10 issues for the audience. For example, this is not an
11 exhaustive list, so how the dosage affect the outcome,
12 and here as you see in the paper one before, how they
13 follow the APP III program, how they model that and
14 incorporate it into their frequent work, and the last
15 one is the patient population level may change. The
16 level of the LDL for patients may change over time.
17 They do talk carefully about that in that paper, because
18 that will affect their estimation. This is actually
19 very important, and I will come back to this issues
20 several times in my comments.

21 So here is my comment. There are four major
22 issues that I want to talk about. One is the selections
23 issues as well as the detailing issues, but I don't want
24 to talk too much about the detailing issues. The other
25 one is the temporal compositions of the sample, which

1 will affect the identification issues of the estimation
2 strategy. The third one is the spacial as well as
3 temporal variations of advertising expenditure, and the
4 last one is patient noncompliance issues.

5 So the first one, the numbers that I have may be
6 a little bit different from the numbers that I talked
7 about, so they start off with 600,000 patients. Now,
8 these patients, they either been diagnosed with this
9 condition, I don't even know how pronounce it, and not
10 diagnosed with that condition.

11 After they diagnosis, they either treat it with
12 statin or not, okay. Now, in his sample he actually
13 focused on that group, so this is a very important
14 issues I guess because as we know, DTC as well as DTP or
15 even whether or not you have insurance or the insurance
16 status that you have may affect the selection of whether
17 you use the drug at all, because remember the first
18 variable that he looked at is how long you're on the
19 drug so before you talk about how long you're on the
20 drug, I want to know whether or not you are on the drug
21 a lot, the take up effect.

22 And DTC definitely affect the pick up effect
23 because I have very short time, so I actually have
24 several slides that talk about a lot more detail how
25 this may actually affect the estimation issues. If I

1 have time at the end, I will come back to that.

2 So let me skip these three slides and go to the
3 second one. The second one is the composition of the
4 sample at each point in time, and so here I would refer
5 to table 3 and figure 1, which I said I ran the data
6 last night, so here the samples span six years, and as
7 you can see people come in at different point in time
8 and increased drastically over this six years, okay.

9 So if you look at the ground which saw before --
10 which you saw before, the LDL levels of this people over
11 time change a lot, and we know that a lot of the people
12 come in -- we have a lot more people come in at a later
13 point in time in their sample, so I really would like to
14 know what is the compositions of these people over time,
15 because even though you're running a regression analysis
16 estimating the DTC effects, remember the questions that
17 I rephrase, what would have happened to this people had
18 they not been exposed to the heavy DTC area, so that is
19 -- I'm not being live in a heavy DTC area, how would
20 that effect my behavior of adhering to the drug as well
21 as whether or not I can obtain the target level?

22 I would like to mention that they actually aware --
23 of the changes in composition issues and they actually
24 put some time into that, but again even running
25 regressions we, would have to keep in mind what are the

1 comparison group that you are using to estimate the kind
2 of actual probability that people had not be exposed to
3 a particular kind of treatment I have five more.

4 I thought we had only five more all together.

5 The third one, the measure of DTC intensity, so
6 this is the definition you have seen before. Actually
7 when I read the paper, I am not very sure exactly about
8 how he defines these variable, so that's why it's up
9 here because this basically is the key variable of
10 interest, so basically he class 88 markets and key
11 periods, so in each -- this is applicable to your local
12 advertising expenditure, so in each of these squares,
13 you have advertising at the local and -- you have the
14 advertising expenditure at the local as well as time
15 period, so he lumps all this together and creates one
16 distribution, and if you're in the top 25 percentile,
17 then you are designated as being exposed to the heavy
18 DTC.

19 So there are I already know which are the 88
20 markets. This is important. This is important because
21 there are three things I would like to know, and I
22 didn't see that in the paper. One is we know that all
23 of these 88 markets are scattered across the entire
24 nations, so the price variation across this nation at a
25 particular -- across this market at a particular point

1 in time may be very, very different, so when we look at
2 say New York and something on -- what is that up there,
3 Washington? So I'm not sure how good is the measure of
4 DTC exposure if you use expenditure, and the DTC
5 expenditure as well could be turning up over time, so
6 these two may have to be taken into account, and maybe
7 we can define this definition.

8 So okay, yes. Because patients -- well the
9 patients enter in say January -- when he observed -- the
10 first time observed me is January 2000, and I'm living
11 in one of those top 25 areas, top 25 percent area. Now,
12 it may be part -- and so it may be possible that my
13 behavior when I go to a doctor this month is actually
14 affect my behavior that I saw the TV previously, in the
15 previous month, so I am sure there are a lot of
16 judgments that you actually have to define as a
17 dependent variable, so this is something that I think
18 has to be thought through about.

19 The last one, which is compared to the
20 selections issue I think is much less important, which
21 is the noncompliance issue, so this isn't so great so
22 I'm wondering whether or not it asks people, have they
23 been picking the drug? No, okay. And have people been
24 using other treatment as well? Because in the paper he
25 described quite well that when people have different

1 high cholesterol levels, what kind of treatment they
2 have -- they can go through, so obviously statin may not
3 be the only one that they go through.

4 So when you want to look at how DTC affect the
5 statin use in terms of affect the health level, other
6 treatment or what we call contaminating treatment may
7 have to be taken into account.

8 So let me refer back to this graph, so whether
9 or not you treat with Statin, you may still be receiving
10 other kind of treatment as well, so when you want to
11 answer the facts of the treatment to statin, other kind
12 of treatment may have to be controlled for.

13 That's all I have. Thanks.

14 (Discussion off the record.)

15 MS. OHLHAUSEN: You're welcome.

16 (Applause.)

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1 PANEL: DTC ADVERTISING

2 MODERATOR: MAUREEN OHLHAUSEN (FTC, OPP)

3 BILL ENCINOSA (AHRQ)

4 Richard MANNING, (Pfizer)

5 JACK CALFEE (AEI)

6 MARTA WOSINSKA (HBS)

7

8 MS. OHLHAUSEN: Well, I think we're going to
9 just launch into our final panel so if the panelists
10 would come and sit up here, I will do double duty here
11 and introduce who they are while they're getting to
12 their spots.

13 We're going to start with Richard -- our first
14 speaker will be Marta Wosinska, she's the assistance
15 professor at Harvard business school. She will be
16 followed by Richard Manning, senior director of
17 corporate policy at Pfizer; William Encinosa, senior
18 economist at the Department of Health and Human Services
19 Agency for Health Care Research and Quality, and then
20 Jack Calfee, resident scholar at the American Enterprise
21 Institute, so, Marta, if you would like to come up and
22 speak from the podium, and I'll hand over the
23 microphone.

24 MS. WOSINSKA: Thank you very much. So what I
25 thought I would do is make two broad comments about drug

1 advertising. I thought I would kind of somewhat to what
2 we saw in the presentations.

3 What's interesting about this conference is how
4 diverse the topics are, and also another thing that kind
5 of stands out so we spent most of the day actually
6 talking about R&D and then in the afternoon we have a
7 small session about just actually direct to consumer
8 advertising and not more broadly about marketing in
9 general in pharmaceuticals, which kind of raises an
10 interesting point: Why is it that direct to consumer
11 advertising has gotten so much attention? And the
12 reason is it's not because it is the largest promotional
13 tool that manufacturers use to market their drugs; it's
14 because it's so extremely salient.

15 And because of the salience, what you end up
16 seeing is that a lot of -- so there's a lot of debate
17 around drug advertising, and there are strong opponents
18 and strong proponents of drug advertising.

19 What I find interesting, and kind of draws a
20 parallel to R&D literature is the sort of struggle that
21 lawyers and economists have around patents. Economists
22 usually would claim not every patent should be of the
23 same length, right, and of the same protection, and
24 lawyers will say, Yeah, but we can only have one type of
25 a patent and we have to figure out the right life and we

1 are going to apply it broadly so there's the same sort
2 of disagreement around drug advertising.

3 People who believe in drug advertising will
4 cherry pick examples where drug advertising has had
5 incredible beneficial effects on outcomes and on
6 patients being treated for certain diseases and whatnot.
7 People who are highly opposed to drug advertising will
8 cherry pick categories that, say toenail fungus, what
9 kind of overall benefit do we have and it adversely
10 effects our health care costs, on the other hand
11 treatment of cholesterol and getting people on
12 medications and in hospitals.

13 So there's a struggle that regulators actually
14 ultimate cannot really sort of apply rules one way the
15 other, but the truth is that there's great variation in
16 terms of where the positive or potentially adverse
17 outcomes occur.

18 Going back to the saliency of drug advertising,
19 perhaps because of that, the focus is usually just
20 solely on that, and it's taken oftentimes out of the
21 context. Again economists have done and a lot of
22 researchers have tried to do a really good job in trying
23 to put it in the right context, so a lot of literature
24 -- there are a number of papers that, for example, will
25 address the fact that direct to consumer advertising is

1 really a mechanism for driving primary demand rather
2 than secondary demand.

3 So it really is not a market share instrument.
4 The effects that have been found have been small, and
5 David mentioned some of that work, but it's really about
6 getting patients into the doctor's offices and getting
7 them brought in, and what this means is return on
8 advertising -- so the incentive for a pharmaceutical
9 company to engage in direct to consumer advertising very
10 much is going to depend on a number of other factors.

11 In particular the return on investment for
12 advertising is going to depend on really what not the
13 current market share is across the market but sort of
14 the market for the new patients that are coming in that
15 are starting to get diagnosed, so if you a new player
16 that comes into the market and doesn't have much of a
17 market share and has won physicians over, they're not
18 going to get much of a return.

19 They'll grow the pie but they will only get a
20 small sliver of it, and as a result, actually the
21 marketer leader might actually benefit very strongly
22 from that, so a good example of this is Lipitor.
23 Lipitor didn't advertise for a year and a half after
24 getting introduced on the market, but it was also one of
25 the largest direct to physician marketing campaigns so

1 the physicians really believed that it was a good drug.
2 Zocor and Prevocal at the time were advertising very
3 heavily.

4 These patients came into the doctors's office.
5 They never saw any ads for Lipitor but the physicians
6 were just putting them on Lipitor, and so it's really
7 Lipitor that benefitted from all of the advertising that
8 Zocor and Prevocal had been doing. At the beginning of
9 drug advertising, manufacturers have been experimenting
10 and now understand that you don't want to go with direct
11 to consumer when you launch a product.

12 You need to make sure that you establish a
13 footing with physicians, and so for example, when you
14 see the statistic, and a lot of people will cite this,
15 three out of four patients who ask a doctor for a drug
16 will get it prescribed. People consider -- people claim
17 this is casualty but in fact it's really a correlation.

18 I would basically say it another way. Companies
19 are smart enough and they will only advertise for which
20 they have won physicians over, and that's why see this
21 kind of high ratio, so there has been work done around
22 that, but there's sort of a number of other elements,
23 and Ginger's, for example, work tries to address some of
24 this, so it's not just physician marketing but there's
25 this learning component as well that plays a role.

1 Advertising potentially might, just as it has
2 been found with detailing. Detailing might get a
3 physician to try a drug, but it doesn't mean that it's
4 going to be widely adopted, and so the learning
5 components are also critical and the findings that
6 learning than advertising is so much more important in
7 terms of what gets prescribed by physicians is key.

8 Another one I wanted to bring up, and hopefully
9 I can do it efficiently here, is basically the whole
10 issue that drug advertising is not the only source of
11 information that consumer have about prescription drugs,
12 so I wanted to show you a couple of slide. F 5 right?

13 I'm just going to touch base on a project that
14 David Bradford and I are working on, and the point that
15 media can also be a very important source of information
16 about prescription drugs. This is a cover from Time
17 Magazine from just before Vioxx -- sometime before Vioxx
18 got pulled off the market, and basically you cannot do
19 this kind of advertising on television or anywhere else.
20 The FDA will not let you do this.

21 This data, this cover, it says "The bad news:
22 Research shows that the disease starts attacking your
23 joints long before middle age. The good news: The
24 latest treatments are more effective than ever."

25 This particular cover is actually in a data set

1 that David and I pulled together on Cox 2 inhibitors so
2 I wanted to kind of just show you, we put together a
3 panel of articles for Cox 2 inhibitors over a five-year
4 period so Celebrex gets launched at this time at this
5 time. There's some media coverage sort of in
6 anticipation of Cox 2 inhibitors. In that five year
7 period we found about 2,000 articles that mentioned
8 these drugs and about a thousand of them talked about
9 the drugs themselves, about their efficacy, and what not
10 and we went through and categorized them in terms of:
11 Were they positive, entirely positive or did they have
12 some potentially negative information? So this is
13 basically how this plays out.

14 There are many more negative articles or sort of
15 semi negative articles in the later time period. What
16 is interesting is what we find is it is not correlated
17 with drug advertising, so when you look at this, there
18 isn't a very strong correlation between drug advertising
19 and so we actually run a regression, the estimates for
20 drug advertising don't really change.

21 What we do find, however, are the following
22 things: Is that DTC and media coverage seems to be
23 working in a similar way. Not surprisingly they are
24 targeting the same person, which is the patient. Both
25 of them seem to be driving visits and neither one seems

1 to have a strong effect on actually market shares of
2 these drugs, but what I think is sort of an important
3 piece of information is this one.

4 What we find is that these effects are actually
5 pretty strong. One positive story is equivalent to
6 about about \$2 million in advertising. That's the
7 estimate that we get in terms of its ability to attract
8 patients into doctors' office, so what this means is
9 sort of an interesting point, so one implication of this
10 is if critics would like advertising to go away, it's
11 not going to really -- the fact that patients are
12 getting information about these drugs from another
13 source means that the problem wouldn't go away, if they
14 consider that a problem. Not only that, it's sort of an
15 interesting and ironic spin on this is here we don't
16 control information. We don't control what the media
17 says.

18 Richard, when he's talking to a journalist, he
19 has to provide the fair balance, but how the journalist
20 is going to use it you have absolutely no control over
21 it. They might not put any of the side effects but they
22 might potentially just write a bad story. That's the
23 problem with public relations, you have no control over
24 what they're going to say.

25 So what you're going to end up getting is that

1 potentially there's an upside to drug advertising in
2 that you actually have control over the message versus
3 you might not in this context, so I wanted to highlight
4 that one has to kind of look at advertising in a context
5 one has to look at advertising in a context rather than
6 in a lump.

7 So I'll pass on the mike to the next person.

8 MS. OHLHAUSEN:

9 MR. MANNING: I thought we had an agreement that
10 the tallest person got to go first.

11 MS. OHLHAUSEN: The person with the earliest
12 flight.

13 MR. MANNING: My flight's earlier.

14 MS. OHLHAUSEN: Sorry.

15 MR. MANNING: That's okay. From the perspective
16 an industry economist, I wanted to show you that I can
17 work a PowerPoint just fine. That was funny. Maybe it
18 wasn't.

19 I want to talk about a couple things. I don't
20 have any analysis to present. I just want to talk about
21 a couple of facts and a perspective at least from my
22 brain about what we should think about and what public
23 policy should focus on about advertising and its role in
24 health care.

25 Down toward the middle. And I guess if you ask

1 me whether advertising ought to be legal or not or
2 whether advertising ought to be restricted, I would
3 have -- I would want to know what's the -- what are the
4 alternatives, what are the healthcare impacts and what
5 are -- what's the measured impact of this behavior, and
6 I think, for example, David's presentation was very
7 useful at getting in that direction.

8 Now, what are the -- what are the impacts and
9 what are the measurable impacts on individual health and
10 healthcare? I think those are the kinds of questions we
11 need to see more of, so I have just a couple facts to
12 put on the table. They're not analysis in any degree.
13 They're just things to think about as policymakers and
14 others go forward thinking about whether or not there
15 ought to be restrictions.

16 The first question, the first fact is that
17 people who probably need treatment very often don't get
18 it. That's been mentioned before, but here across about
19 ten or more categories of disease, we have rates of
20 treatment. Now, the blue line, the blue segment of
21 those lines for each of those conditions represents the
22 share of the population that has the condition that's
23 undiagnosed. The gold line, gold segment is diagnosed
24 but untreated or not fully treated, and the yellow
25 segment, in many cases a small part of that bar, in some

1 cases a larger part represents the share of the
2 population that is treated to an appropriate medical
3 target.

4 So the first fact is that there's -- while
5 there's a great deal of concern that advertising might
6 drive over utilization, there's also a baseline reality
7 that there's a good deal of underutilization for
8 important medical conditions.

9 Another important thing that's been mentioned
10 but I would like to just drive home is that even people
11 who are treated very often stop treatment before they
12 should, so we've got three conditions listed here but
13 you could do this for a number of other conditions, for
14 high cholesterol, high blood pressure, diabetes. After
15 about 18 months roughly half of the people had stopped
16 taking the medication. Now, for some people maybe
17 that's okay but for most people that's a problem. If
18 you've been diagnosed and a doctor has determined with
19 you that you should be on this therapy, after 18 months
20 you should still be on that therapy, at least for these
21 conditions. The fact that you fall off the therapy
22 means that something has gone wrong in the information
23 flow of medical care.

24 One of those things that has gone wrong at least
25 according to I think it was the Harris and Racket pool

1 is people forget to take there medicine. Harris asked
2 about a bunch of people, well, if you're not adherent
3 and you've quite taking your medicine, why not. The
4 most common response was I forgot, so there's an
5 information problem, people either not remembering or
6 not understanding why it's important to stay on their
7 medicine.

8 At any rate one of the serious barriers to
9 staying on therapy is information problem as much as an
10 economic or as much has a financial problem, so that
11 advertising may be one way to address those kinds of
12 concerns.

13 The last thing -- I'm just going to skip to the
14 end of this, the last point to make is there's a common
15 perception, at least I run into it all the time and
16 maybe that's because I run into hostile audiences, but I
17 run into a perception that marketing is all powerful and
18 all a company has to do is put a product on the market
19 and advertise it and promote it to doctors, and it will
20 be a blockbuster, and therefore there's something wrong
21 with advertising because that's all you need to do to be
22 successful is to market something.

23 So just here is a sample of one. The T
24 statistic is not there because you know there's no such
25 thing when you only have a sample of one, but a sample

1 of one, just to illustrate a failure, and I'm sorry to
2 pick on a competitor, but a failure of an attempt to
3 bring a new product to market through a marketing
4 effort.

5 The yellow line represents the sales of daily
6 Prozac or Prozac as it was approaching patent
7 expiration. At some point around here, the patent
8 expired. The sales of the daily formulation fall off
9 the cliff. There is a weekly formulation developed,
10 sales represented by this blue line, a relatively
11 aggressive marketing campaign, \$32 million direct to
12 consumer advertising campaign, a little larger than the
13 DTC that was going on for the daily formulation, and the
14 weekly formulation just didn't takeoff.

15 It never achieves success. The generic
16 formulations of daily generic fluoxetine take over this
17 market. And again one experience doesn't tell an entire
18 story, but it does put a bit of a light to the idea that
19 many people unfortunately hold that all a company has to
20 do is market something and it will be a success, so with
21 that, time is probably already well spent. I just want
22 to leave those things on the table for thought and maybe
23 for future discussion.

24 MS. OHLHAUSEN: Do you want me to put yours up?

25 MR. ENCINOSA: So far the literature on

1 advertising has looked at the impact of advertising on
2 treatment efficiency, so I think the next step for the
3 field would be to look at how advertising impacts
4 pricing efficiency, so I'm going to look at preliminary
5 results that I have so the main problem with prices is
6 price dispersion, each drug may have several different
7 prices on the same market.

8 For example, sometimes they don't have a lot of
9 dispersion. This is a cross 200 markets, 45 employers.
10 These are insured people. 90th to 10th percentile in
11 pricing. Lipitor, there's only a \$60 difference. You
12 move up to Prozac, it's a hundred dollars. You move up
13 to a painkiller, OxyContin, it's \$200, so there's a lot
14 of price inefficiency. The data that I'm looking at, 45
15 employers, we're looking at about 728 million drug
16 claims, 20 therapeutic classes.

17 So it's well known in the Sorenson paper that
18 price shopping incentives often lower this dispersion
19 such as higher cost sharing, higher coinsurance rates,
20 so the big question here is: Does advertising have some
21 kind of price shopping effect?

22 Of course there's no pricing information in the
23 advertisements, but if this advertising is really
24 encouraging patients to seek out these medications, the
25 next step is for them to look at: Well how much does it

1 cost? Especially when you're getting the marginal
2 patient, maybe the low income patient, you really want
3 Lipitor now he needs to find out how expensive it is.

4 Now these are two measures of price dispersion.
5 You can see they decline with advertising levels. Now,
6 the top five advertised therapeutic classes are at the
7 top, and it turns out they have the lowest coefficient
8 of variation. The coefficient of variation is the
9 standard deviation divided by the price. Some of the
10 unadvertised medications had higher coefficients of
11 variation so we see in the raw data that there's
12 something going on.

13 Now, we checked this out using a regression
14 method. We used market fixed effects. We purged the
15 pharmacy prices, the pharmacy fixed effects to get rid
16 of attributes of the pharmacy so we simulate an increase
17 in advertising from the 20th -- 25th percentile to the
18 75th percentile of advertising, and we see that these
19 are significant effects. These are three different
20 measures of dispersion. We see that as you increase
21 advertising, the dispersion, and the prices decreases.

22 Now, what's the magnitude of these? These
23 effects are pretty low compared to other price shopping,
24 incentives. When we increase the coinsurance rate, this
25 is a pretty big effect. Increases it lowers the

1 dispersion by 23 percent.

2 When we move from product medications to acute
3 medications, this increases the dispersion. This is
4 antibiotic medications. People don't purchase them that
5 much for acute situations, so they don't shop for
6 prices, so you can see how that would increase the
7 dispersion.

8 When we move from salaried workers to hourly
9 wage, we're in essence lowering the income. As you
10 lower income people have to shop a lot more, and that's
11 about a 10 percent effect in lowering the decides
12 percent and the prices. Now, price shopping usually
13 lowers the profit margin.

14 Now, with these other shopping incentives, we do
15 see that when you're increasing coinsurance, the profit
16 margins decline, so as advertising following a price
17 shopping model, it doesn't look like it's going in the
18 right direction. The increasing advertising actually
19 increases the profit margin.

20 So to conclude we see that advertising does have
21 some kind of effect on prices. It's decreasing the
22 dispersion of prices. So we don't know really what's
23 causing that. It doesn't look like it's actually price
24 shopping because the profit margin still increase, so
25 that's what we have. This is a preliminary analysis.

1 We would encourage other people to also look at how
2 advertising affects prices.

3 MR. CALFEE: Thank you. I don't have a
4 PowerPoint.

5 MS. OHLHAUSEN: Bless you.

6 MR. CALFEE: I am speaking from notes, so I'm
7 going to stand here dramatically in the little of the
8 floor. I'm Jack Calfee from AEI, but I was once an
9 employee. I begin my professional life in the bureau of
10 clicks at the FTC, so it's nice to be back, different
11 building but same intellectual environment.

12 I want to say a little bit about ways in which
13 to put the stuff we've been listening to today into
14 context, both the kind of research that's being done and
15 the results that we've seen. I've been to a lot of
16 conferences and meetings and so on on DTC advertising.

17 This is the first one I've before been involved
18 in that no one has mentioned, at least barely mentioned
19 fair balance, risk information, FDA rules, which
20 companies have been investigated for ads that have not
21 met FDA's standards and to so. This is really phase II
22 of DTC research.

23 Phase I consisted almost entirely of survey
24 research, and that was inspired directly by the FDA's
25 rules, and some of that research was commissioned by the

1 FDA and other sources and so on, and we're notice in
2 phase two because the econometricians have pretty much
3 taken over from the survey researches so we're looking
4 at market data, et cetera, which brings me to
5 advertising research generally.

6 There's been a fair amount of economic and
7 econometric analysis of advertising over the years, but
8 it has been very highly concentrated in a very small
9 number of markets. All of those markets are ones that
10 are controversial. There's a lot of research on, for
11 example, tobacco advertising, alcohol advertising,
12 health claims for foods and also back in 1970s
13 advertising for professionals optometrists, lawyers,
14 doctors, et cetera from an antitrust point, primarily
15 rather than whether the advertising was deceptive, et
16 cetera.

17 This is yet another example of the focus on a
18 controversial form of advertising so we're seeing a huge
19 amount of advertising -- of research on DTC advertising,
20 not very much research on advertising for say doctors,
21 and I'll get back to that later or advertising for HMOs,
22 health care providers, et cetera.

23 In this history of advertising of controversial
24 market, the usual finding or in fact the dominant has a
25 strong effect on market shares or brand shares and no

1 effect on the overall level of sales or activity which
2 -- and usually the purpose has been to discover the
3 effect on overall sales because we're talking about
4 tobacco, smoking, alcohol, drinking, et cetera.

5 The other results are quite different. The
6 results so far are finding an effect on overall markets
7 but not on brand shares, et cetera. It's a different
8 environment. Now, when people talk about why is it that
9 tobacco advertising doesn't increase smoking and alcohol
10 advertising doesn't increase drinking. The usual answer
11 is, well, those are a mature audience, there's not
12 really much for people to know that they don't already
13 know about those product and that's why the effects are
14 pretty much or almost entirely at the brand level.

15 Here we have a market that's really not mature
16 but in a very fundamental sense because pharmaceuticals
17 are not, A, marketed, at least not from the idea of
18 promotions. There are a whole series -- well, sort of
19 tiny markets but Lipitor and the statin market is pretty
20 big at this point, 10, 12, 15 billion, whatever it is
21 for statins, but each market is its own market.

22 The market for rheumatoid arthritis drugs has
23 nothing to do with the market for statins or the market
24 for PPI, anti-ulcer drugs, et cetera, and within each of
25 those markets for the most part you do not have in any

1 sense a mature market. The closest would be maybe the
2 antiulcer drugs, which is maturing and is now rapidly
3 disappearing except for Nexium from consumer advertising
4 but these are mostly new markets.

5 So advertising here is effecting -- is working
6 pretty much the way you would expect for a new market,
7 and what we're seeing is a transition from one market to
8 another market to another market as another market comes
9 into you being, and I just mentioned for example the TMF
10 inhibitors for rheumatoid arthritis.

11 Now, to me the interesting things, the puzzling
12 thing about this, and I speak as someone who has been
13 looking at this and working in this more or less since
14 DTC began to become really prominent and controversial
15 in the late '90s and by the year 2000, et cetera. I'm
16 having trouble rejecting the hypothesis that DTC
17 advertising is not a big deal in the pharmaceutical
18 market.

19 I mean, we know that we have a market now that's
20 in the order of 200 to 250 billion dollars. Part of
21 that market is inherently unsuited for DTC, and so it
22 should be excluding. I'm thinking of the market for
23 maybe Epogen or something like that, unless the
24 performance enhancement part of it takes off, but that
25 hasn't happened, at least not explicitly.

1 But when you say an advertising to sales ratio
2 in the order of 2 percent or so, it's hard to resist a
3 conclusion that the manufacturers who are allocating 2
4 percent on average of all revenues are not getting
5 tremendous returns from this kind of advertising except
6 for very selected categories and a very selected number
7 of brands.

8 And although the advertising has been going up
9 pretty rapidly, it really hasn't been going up any more
10 rapidly than the pharmaceutical sales at all, and again
11 I'm having trouble rejecting the hypothesis that this is
12 a relatively small change in terms of the overall
13 pharmaceutical market. It's a big deal in the since
14 that DTC advertising presents a very, ripe political
15 target, and it certainly is attracting a lot of
16 criticism of the industry.

17 And it's amazing how much attention when it's
18 focused on the pharmaceuticals and the industry what
19 might be wrong and so on, how much of that tension
20 either focus on DTC advertising or uses DTC as a sort of
21 taking off point in the criticism, even though the truth
22 is that DTC doesn't really have much to do with whatever
23 it is that most people think is really important or even
24 worth worrying about in the pharmaceutical market.

25 One final comment, and then I'll get out of here

1 because it's five o'clock and I'm the only thing between
2 you and rushing out to get a taxi, and that is we have
3 seen when the FDA changed its -- while they didn't
4 change anything except their interpretation of the
5 regulations in 1997, although they've done a little bit
6 more than that since then, but when they made that
7 rather dramatic change, this created what a lot of
8 people have seen as a very useful and very interesting
9 natural experiment which has generated a lot of research
10 that you have seen today, and even today a lot of the
11 DTC research starts before 1997 so you can see what
12 happens as a result of that change.

13 But there's another natural experiment that's
14 been almost completely ignored, and that is although
15 it's been mentioned, and that is comparing the
16 advertising that's regulated by the FDA compared to the
17 advertising that's not regulated by the FDA. FDA does
18 not regulate medical device advertising, for doctors,
19 clinics, hospitals, et cetera.

20 With the results of that advertising, it looks
21 very different from the advertising that we see for
22 pharmaceuticals. You don't see the risk information.
23 When I see an ad from Sibley Hospital, the one's whose
24 orbit I happen to be in, it has a lot of wonderful
25 things mentioned about Sibley Hospital. Never once have

1 I seen any of those brochures, et cetera, mention that
2 if you actually get admitted to Sibley Hospital, your
3 chances of getting a life threatening infection are
4 greater than they ever were before you stepped in that
5 hospital.

6 That kind of information you never see and I
7 hear ads for MRI machines and stuff like that. There's
8 nothing wrong with the ads. I think some of them are
9 useful but there's none of the risk information that
10 we're seeing, and it raises a natural question as to
11 whether or not there's a difference in how advertising
12 works in these markets with one set of rules for
13 advertising in markets and another set of rules.

14 And among the other puzzles that at least pop up
15 in my brain when I compare these different parts of the
16 advertising business are mysteries about why it is that
17 although I just claimed that the volume of DTC
18 advertising is relatively modest compared to advertising
19 compared to the scale of the market, the volume of that
20 direct to consumer advertising for doctors, hospitals
21 and clinics is really small when you consider the size
22 of those markets, and I'm not sure why that is.

23 I know part of it is that advertising tends to
24 work best for branded products, especially ones that
25 have national brands, and you get that far more with

1 pharmaceuticals than you do for health care and so on,
2 but there are some national brands in healthcare. There
3 are national brands in products and devices, et cetera,
4 that are not getting anywhere near the volume of
5 advertising which tells me again there's something
6 specific about pharmaceuticals that's different from
7 some of these other products.

8 And so as we explore pharmaceuticals, and we
9 explore DDT advertising and son, I think there's still
10 something interesting questions to be asked as to what
11 it is that makes this actual -- this very kind of
12 advertising apparently fundamentally different from the
13 advertising we see in other parts of the market, and
14 those are my comments.

15 (Applause.)

16 MS. OHLHAUSEN: Chris do, we have time for a
17 couple questions?

18 MR. ADAMS: I'm sure.

19 MS. OHLHAUSEN: Since I'm the moderator I will
20 actually ask the first question which is I think from
21 the data that we've seen today, I would believe that
22 it's probably premature to say DTC advertising should be
23 prohibited but based on the data, do you all have any
24 views on whether there should be changes in how it's
25 regulated whether changes to lessen the regulation or to

1 tighten the regulation?

2 MR. CALFEE: I have certainly seen no evidence
3 to suggest that DTC advertising is under regulated
4 considering these other areas such as doctors and
5 hospitals and so on have vastly less regulation, and
6 there's little, if any, evidence that there are any kind
7 of problems from that kind of advertising.

8 MS. OHLHAUSEN: Anybody else?

9 MR. MANNING: I'm sure my views are perfectly
10 predictable, but I think another thing you might want to
11 look at is whether or not advertising is drawing the
12 right kind of people into a physician's office. There
13 are some surveys by the FDA that find roughly 90 percent
14 of the people who go in and ask about a specific drug
15 have the condition that that drug treats, so that would
16 indicate that in fact you're not getting the wrong
17 people in the office, so I guess my answer would be I
18 don't see the need for major rewriting of the
19 regulation.

20 MS. OHLHAUSEN: You don't think it's too strict.

21 MR. MANNING: I don't think it's always -- do I
22 think the regulation is too strict?

23 MS. OHLHAUSEN: Right. What I asked is should
24 it be changed one way or the other?

25 MR. MANNING: I would stay where we are if we

1 had to -- my guess is that if I put it up for change, I
2 wouldn't win.

3 MS. OHLHAUSEN: Anybody else want to comment?

4 MS. WOSINSKA: One comment I was going to make
5 about the regulations. The regulations aren't extremely
6 precise which is what actually a lot of advertising
7 agencies find very frustrating. There are broad
8 guidelines for what you can and cannot do, so should
9 they be changed, they're relatively broad that they
10 occasionally get clarified.

11 So one would really have to talk about a major
12 change because right now the system is set up in such a
13 way that there's room for just slight renegotiation of
14 things, so by design, they have room to wiggle with, but
15 from my perspective as an economist again, I do believe
16 -- I believe that there's such a variation across where
17 there benefits and where there aren't, SO it's
18 problematic to be applying strict rules across the board
19 to everyone when the benefits and the costs really vary
20 across.

21 And there are other mechanisms for which the
22 downsides of the concerns can be mitigated such as
23 excluding drugs that are advertised from formularies,
24 and whatnot so there are either mechanisms that can
25 mitigate some of these concerns.

1 MR. CALFEE: Can I add something to that? My
2 sense is that there's two basic criticisms that one has
3 to worry about in connection with DTC. One is that they
4 may get -- they may cause a safety problem. People are
5 using drugs that are less safe than they should be and
6 the other is they're causing the healthcare system to
7 spend drugs that aren't worth what they cost.

8 The worth question I think the critics had a
9 great deal of difficulty nailing anything done in DTC,
10 there has been a lot of anecdotal stuff, but even with
11 the Vioxx thing along with SSRIs and so on, it's proven
12 to very difficult to actually come up with any
13 compelling story that DTC advertising has really imposed
14 a significant extra risk on people, especially when you
15 compare it with the benefits people often get out of
16 these products.

17 The question of whether or not advertising
18 induces demand beyond an official level, that's a very
19 very different question and it's much more difficult to
20 answer, and it's much more plausible to think that,
21 yeah, we are getting some insufficient use for the
22 reasons Ernie Brendt mentioned earlier as long. As
23 people aren't paying for their own products there is a
24 moral hazard, and you're going to get some over usage of
25 a product.

1 Now, it's very hard to regulate advertising in a
2 way that deals with that problem as opposed to leaving
3 the other actors in the system such as PBMs and the
4 healthcare payors and so on to deal directly with what
5 kind of drugs they're going to pay for, et cetera, but
6 it's a very difficult and differing problem.

7 MR. ADAMS: Thanks. I just want to thank
8 everybody for making it through the day, and I also want
9 to point out that there are other people here that you
10 might be interested in talking to. We have
11 representative from Merck. We have Kit from FDA who
12 does a lot of DTC advertising stuff, so please go and
13 talk with them if you want to, and again thank you to
14 everybody and thank the panel.

15 (Applause.)

16 (Whereupon, at 5:10 the workshop was concluded.)

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CERTIFICATE OF REPORTER

DOCKET/FILE NUMBER: P065800
CASE TITLE: ROUNDTABLE ON THE ECONOMICS OF THE
PHARMACEUTICAL INDUSTRY
HEARING DATE: OCTOBER 20, 2006

I HEREBY CERTIFY that the transcript contained herein is a full and accurate transcript of the steno notes transcribed by me on the above cause before the FEDERAL TRADE COMMISSION to the best of my knowledge and belief.

DATED: NOVEMBER 8, 2006

DEBRA L. MAHEUX

CERTIFICATION OF PROOFREADER

I HEREBY CERTIFY that I proofread the transcript for accuracy in spelling, hyphenation, punctuation and format.

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