

# “So Close”

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Good afternoon, Ladies and Gentleman – and thanks to the Massachusetts Biz-Bio coalition for inviting me.

I’ve really been looking forward to this event. I was born in Louisville ... went to college in Cincinnati ... and of course have lived in Indianapolis now for a long time ... but Boston is like a second hometown to me. I earned a Ph.D. in chemistry here ... and have kept strong ties to Harvard. It’s where I spent my first four years of married life, and where our oldest son was born.

It’s also been my privilege – over the years – to get to know quite a number of your government and business leaders here in Massachusetts. This state really stands out for the approach that you’ve taken to developing the life-sciences sector – encouraging investment ... and capitalizing on the talent that’s associated with your great universities and medical centers.

For that reason, when I was asked to reflect on the requirements of innovation for this event, it was clear to me that I needed to aim very high.

The pharmaceutical business is, I believe, a hugely misunderstood part of the global economy. So it’s not uncommon for me to present what amounts to an undergraduate course on the life sciences.

In those settings, I try to educate folks about the enormous complexity, risk, and cost of developing new drugs. And I go into detail on the “three-legged stool,” if you will, that allows the drug-development model to work. The three legs are:

- market access ... the ability to make our products available to prescribers and patients – which is far from straightforward in many cases;
- pricing freedom ... the ability to obtain prices that let us recoup the huge cost of development; and ... perhaps the most basic requirement of all ...
- intellectual property protection ... without which the incentives to take financial risks on health-care R&D simply would not exist.

I feel pretty certain that this audience understands those things.

At other times, I'm asked to speak in communities that are trying to build up their life-sciences sector. Those situations call for the "graduate course" on encouraging innovation – where I tend to talk about the importance of securing a critical mass of talent ... along with ways of distinguishing a region in the competition for private investment.

Boston is usually one of my case studies for that speech, however – so I won't stand here and lecture you about the things you're already doing at a very high level.

Greater Boston is second only to San Diego in the Milken Institute's ranking of life-sciences clusters. The economic impact of the biotechnology and pharmaceutical industries in Massachusetts is more than \$5 billion a year ... and – according to reports from Northeastern University, the state's employment rolls in biopharmaceuticals grew by more than 10 percent in the first half of this decade ... while they were declining by 25 percent in manufacturing sectors overall.

Clearly, you've been doing the right things to encourage this level of economic impact and growth ... on top of an already significant base in the life sciences.

So the graduate course is not appropriate either. This event calls for nothing less than the "postdoctoral seminar!" I'll warn you ... it's a work in progress, as most postdoctoral seminars are. The professor ... in this case ... is learning right along with the class – and he's probably behind them on a number of levels.

Let me tell why I think that it's time for a postdoctoral approach to looking at the requirements of innovation in the life sciences – and not only in Boston.

In a nutshell: I believe that we are being challenged as never before, to make policy decisions about a very wide range of issues that will determine not just the location ... but also the speed, quality, and course of innovation in the life sciences.

Government and public policy will be the focus of much of this decision-making – but when I say "we" are being challenged ... I'm deliberately trying to capture the responsibility of leaders in business, science, academia, and in the advocacy community ... to step up and be heard.

There's so much at stake.

The life sciences – from the decoding of the human genome ... to new information about disease pathways ... to the application of information

technology – have experienced a Golden Age of discovery in recent years. There’s been so much new information, frankly ... and so many new tools ... that most of it is still waiting to be interpreted, integrated, and applied.

Today, I’m confident in asserting that more information ... more raw data ... about the workings of the human organism and the origins of disease is sitting on proverbial shelves ... than had even existed in the last millennium.

Take a look at this chart from a presentation given by Steve Burrill [reference to slide], a highly informed optimist about the life sciences, which is the best kind of optimist. Using simple language, Steve charts out the truly millennial nature of the change that most of us may live to experience – towards highly personalized therapies ... longer and longer life spans ... real-time diagnosis and treatment ... and prevention rather than waiting for a disease to take its toll.

As a society, we are so close ... so close ... to realizing the most extraordinary breakthroughs of all time in human health – if we don’t mess up!

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This is a chart I rarely show externally [reference to slide]. It’s a current list of all the molecules in development at Lilly, which have reached the stage of testing in people. Don’t worry ... I won’t give you the rundown on all of these compounds. That would really turn this talk into a post-doctoral seminar! Even “as is,” however, this chart sheds light on our topic in a number of ways.

First, I believe that it reinforces the point I just made about the prospects for advances in treatment. This list of molecules in human testing is larger than it has ever been in the history of Eli Lilly and Company. Last year alone, we moved 16 new molecules into initial clinical testing – nearly doubling the size of that portfolio – and we’re expecting to add 15 more this year. This tells me that our scientists are starting to connect the dots ... between the discrete insights and data points uncovered in recent years.

There’s another thing that might jump out at you about this chart. The new molecules listed in yellow type are large molecules ... biotech compounds. Yes ... about one-third of the new molecules in development ... at this seemingly traditional, “Big Pharma” company ... are biotech molecules.

The boundaries between pharma and biotech are blurring, for very good reasons. Science is pulling us in that direction, for one thing. Large molecules often are tolerated better by patients ... and more effective than traditional chemistry-based compounds. It is proving easier to “tweak” large molecules early in the development process ... to knock out elements that are

linked to harmful side-effects ... or to tailor molecules more precisely to particular disease variations or patient groups.

There's one last thing I want you to notice on this chart. You do not have double vision, but you are seeing some labels more than once. We've put the name of the disease target up there in some cases ... rather than the name of the molecule itself. These are all different molecules, but you'll see cancer several times ... ditto for obesity and osteoporosis and rheumatoid arthritis. And you'll see diabetes over ... and over ... and over again.

The explanation is not that we're producing a bunch of me-too drugs ... all basically the same. The real explanation is quite the opposite. Lilly is committed to pursuing what we're calling "tailored therapeutics" – products that reflect the scientific insights of recent years in a manner that makes them more consistently effective ... in ever more precise groups of patients.

That means pursuing multiple avenues against the same disease – not only because some of these therapies will fail in the clinic ... but also because some of them may work in one group of patients ... but not in others. Some may play a role at an early stage of a disease ... but not at a more advanced stage of the same disease.

It's true that some aspects of personalized medicine have been going on for quite some time, but the industry is making a quantum leap today. In Lilly's case, tailoring is not the new buzzword of the year. It's the vision we've set for our company's very existence in the years to come. Optimal outcomes for individual patients: that's our vision ... and realizing that vision will mean changes in every part of our business. We know that.

This chart changes every month, by the way – for several reasons. New molecules move into the clinic, as I said. That's the good kind of change. But other molecules fall out of the pipeline ... if they do not work as we hoped ... if they have unexpected or unacceptable side effects ... or if, in the end, regulators do not agree with our conclusions.

This chart from the *Wall Street Journal* [reference to slide] paints a sobering picture – and introduces a key paradox. It's been a Golden Age of science, as I said. Pharmaceutical companies are spending more than ever to bring each prospective therapy forward. And yet ... the number of regulatory approvals in recent years has gone down. Down ... not up.

There are some good explanations for this paradox – and, in my view, these explanations need to be at the center of how we think about policies to support innovation in the life sciences.

First and foremost, I want to be clear that Lilly is committed to patient safety. However, I'll acknowledge at least one of the conventional explanations, which is that the FDA and other regulators have raised the bar on drug safety to an unusually high level. The growing number of "approvable letters" versus approvals, I believe, bears that out ... as well as the large number of so-called "black box" warnings in drug labels that have been required by the FDA in recent years. The allegations in the Vioxx situation and other high-profile cases have made regulators very skittish about allowing benefit to trump risk, even though no medicine is completely safe and free of side effects.

But let me ask you to keep three other explanations for the approval slump in mind, which I believe are more compelling and ultimately more useful in suggesting policy moves.

Number One: It's quite possible that regulatory approval of new molecules is a lagging indicator ... during the kind of revolutionary transition in science that I've been talking about.

For several years, as we've struggled to make sense of insights from the Human Genome Project and many other breakthroughs in basic research, it's not surprising that there would have been a kind of "creative pause" in early-stage development. And a pause in yesterday's early-stage development ... means a slowdown in today's new-drug approvals.

Think back on the large ... and growing ... early-stage pipeline at Lilly that I showed you a moment ago. It should portend – we obviously hope that it does – a flurry of approvals just a few years down the road ... now that we're starting to make sense of all that we've learned.

A second thing to keep in mind: More data and more knowledge make for better products in the long run ... but they do not necessarily help to bring new therapies to market more quickly or cheaply. In fact, the opposite appears to be true if you look at recent history.

As this chart shows [reference to slide], the cycle time for drug development has increased in each of the last four decades. Dealing with increasing volumes of data ... and the growing complexity of drug development ... has required more time and more money. It should be possible to reverse or at least arrest this trend – I'll talk about that more in a moment – but not through business as usual.

The third factor to keep in mind: In any given week, you can hear me ... and others, I hope! ... reminding folks inside Lilly that if we're going to realize our

vision of delivering more optimal outcomes for individual patients ... every part of our operations needs to be transformed – R&D, of course ... but also manufacturing, external partnering, and sales and marketing.

Well, the same can be said about the larger health-care system. And so far, not enough has happened by way of serious coordination between these players ... let alone systemic transformation to realize the advantages of personalized medicine ... and to deal with its uncertainties.

Think about it. What if we could speed up the dissemination of new knowledge to doctors ... so that the quality of care goes up? What if we could improve patient compliance with treatment in significant ways? What if there was a comprehensive and reliable feed-back mechanism ... to detect safety signals as well as the unexpected benefits of therapy in the actual practice of medicine?

Biotech and pharma companies alone cannot make any of these things happen. It takes the engagement of many other players – and some enlightened public policy.

If these things did happen, however, does anyone doubt that we'd see more approvals of new therapies ... and more willingness to trust the system of care ... rather than the efforts of regulators to anticipate every risk ahead of time?

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In my last few moments, I'd like to focus on some of the tangible contributions that public policy could make ... in helping to realize the enormous promise of innovation in the life sciences.

Let's do this by recalling the various explanations for the recent slowdown in regulatory approvals.

Think about what's needed to master the new knowledge, the new tools, and the vast complexity of health-care R&D today. It's like the old line about what makes a retail business successful ... three things: location, location, and location. Well, if you ask me what makes a life-sciences business successful, I'd say ... three things: talent, talent, and talent.

So here are some things ... that policy can do to boost the talent pool.

We could start by fixing our country's immigration system ... so that it's easier for companies to hire top-notch talent from abroad. Since the start of 2007, Lilly has hired exactly 112 high-level research scientists to work in the

U.S. Of those, more than a quarter – 30 of them – came from other countries. A source of more than a quarter of your supply of anything ... is a source that you depend on. And yet, federal policy is not an ally ... it's a hindrance. Bringing those 30 on board was like pulling teeth.

That's actually a charitable analogy, since you can get a tooth pulled pretty quickly! There's simply no excuse for the sluggishness, cost, and complexity of our country's visa system; it diminishes our nation's attractiveness to innovators and entrepreneurs – just when we need them most. At the end of the day ... if the best talent cannot come to the U.S. ... then it will go elsewhere, much to the detriment of our businesses in the life sciences.

Now, if policymakers lament the fact that more Americans are not being hired as scientists and engineers into the life sciences ... fine, let's focus on that as well. Science education at the primary and secondary levels in the U.S. does not measure up to what's available to kids in dozens of other countries ... and the results are reflected in standardized comparisons.

This also is not a time to shortchange public investments in basic research. There should be increased funding of groups such as the National Institutes of Health and the National Science Foundation ... which form a vital synergy with private industry. The academic sector often supplies the raw material ... such as the insights on disease processes and leads on prospective molecules ... which industry then works to develop and commercialize.

Public funding of basic research is a classic “exponential investment.” It's not just the new insights these efforts generate ... it's the experience that is gained by thousands of scientists, some of whom may stick with basic research in government labs or universities ... while others will apply what they've learned in industry.

With regard to drug development cycle times, there are a couple of important policy considerations.

The first is really an infrastructure challenge for drug developers and for regulators as well. Developers need to use information technology in more aggressive and sophisticated ways ... to speed up the collection of data and to store and manipulate it more effectively.

The growing use of adaptive clinical trial designs – aided by information technology – is one encouraging sign on this front. So is the trend toward shared databases of tissue samples, imaging data, and other tools across industry and academia. There's a lot of this happening in research on Alzheimer's disease, for example.

The notion of “virtual” drug development teams – powered by the Internet – also holds a lot of promise. Lilly has managed to speed up a number of molecules with our so-called “Chorus” platform – which we use for early-stage collaboration with individuals and groups outside the company.

For their part, regulators need to become more transparent in their expectations and requirements of developers ... and to undertake their own, ground-up reappraisals of how they get things done. Last year’s PDUFA reauthorization sets the right performance goals for FDA in responding to new drug applications and the like ... but major changes in day-to-day operations and staffing will be necessary to achieve these goals.

The increase in drug-development-cycle times makes another policy consideration crystal clear: this is not the time to weaken intellectual property protections on medicines in any way. The window of time for recouping massive R&D investments is already quite short. If it closes any more, then the rationale for investment will simply collapse in many cases.

It’s this consideration that makes the current debate in Washington about so-called “follow-on biologics” so critical. If there is to be a new regulatory pathway for attempted duplications of biological products – the biotech equivalent of generics – then it needs to protect patients above all ... while guaranteeing a decent period of intellectual property protection for the developers and manufacturers who are taking the enormous financial risks.

It can be very hard, as you may know, to create precise copies of biological products. Everything from the origins of cell lines to the details of the manufacturing process can result in slight variations ... which in turn can have not-so-slight implications for a product’s effectiveness and safety.

This certainly hit home right here in Massachusetts just a few days ago, when the FDA rejected a request by Genzyme ... here in Cambridge ... to manufacture one its own biologic drugs at a different plant – because of small differences in chemical structure that would have resulted.

So ... it’s clear that any new legislation needs to define a rigorous approval process for bio-equivalents.

At the same time, if we want to sustain the flow of R&D investments to places such as Boston ... and the flow of new biotech products to patients ... then a follow-on biologics regime needs to establish a reasonable period of so-called “data exclusivity” for the original manufacturers. At least 14 years is needed – barring a dramatic acceleration in those cycle times you saw – if the basis for investment is going to be secured.

Considerable experience now shows that 14 years is about the minimum amount of time needed – not only to recoup initial investments ... but also to provide incentives for the funding of follow-on clinical trials – to test products for additional indications ... against new disease targets. This is especially true with regard to cancer-fighting agents ... whose potentials are often revealed only in clinical practice.

Data exclusivity means that data about a product and its manufacturing process cannot be used by another party as the basis for an approval request. It's a much cleaner approach than traditional patenting – under which a patent-holder's right can be, in essence, continuously litigated ... creating enormous uncertainty. Data exclusivity leaves no doubt as to ownership during its run – and when it expires ... it expires – clearing the way for a less costly alternative.

Several member of this state's congressional delegation have played very constructive roles in helping to craft follow-on biologics legislation that meets these standards ... and those of us building businesses around biotech products certainly wish them Godspeed!

I would urge all of you to make your views known in Washington on this issue. In Massachusetts, your legislature is about to make a dramatic, \$1 billion public investment in the life sciences – through tax incentives, grants, and capital projects. That gives you an even larger stake in protecting the ability of biotech businesses to succeed ... which is the basis of our ability to create jobs.

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Ladies and Gentlemen: One way or another, the need for this kind of “post-doctoral seminar” will not continue indefinitely.

Either we will stay the course as a society ... sustaining the basic requirements for innovation in the life sciences ... and improving the conditions under which talent and investment are attracted to R&D in biopharmaceuticals. Or ... whether it's by neglect or piecemeal dismantling or failure to change the things that need to change ... we will put the entire enterprise at risk.

The profound contrast between the breakthroughs in human health that we can secure ... and the relentless efforts to kick out the “three-legged stool” of market access, pricing freedom, and intellectual property protection ... leads me to see the situation as just that delicate.

Let's work to keep the fundamental requirements of life-sciences innovation in place ... and to steer those "relentless efforts" in the direction of attracting talent to these pursuits ... realizing the promise of biotech ... tailoring new therapies ever more specifically to individual groups and patients ... and enlisting the entire health-care field in achieving better outcomes for patients.

We're so close. Let's get it right!

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