

HEARING TESTIMONY

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Chairman Pitts, Ranking Member Pallone, and Members of the Committee, my name is Jonathan Leff. I am a Managing Director at Warburg Pincus, where I am a member of the firm's Healthcare Group. I joined Warburg Pincus in 1996, and for the past 12 years, I have led the firm's investment efforts in biotechnology and pharmaceuticals. Established more than 40 years ago, Warburg Pincus has invested over \$7.5 billion in more than 130 healthcare companies. I personally have more than 15 years of experience investing in innovative life sciences companies and have served on the boards of more than 15 companies involved in developing novel therapies for a wide range of diseases. I am also a director of the Spinal Muscular Atrophy Foundation and a member of the Executive Committee of the Board of Visitors of Columbia University Medical Center as well as a member of the Board of Directors of the National Venture Capital Association (NVCA) and of the Biotechnology Industry Organization (BIO) Emerging Companies Section Board.

It is my privilege to be here today to share my perspective as a venture investor on the impact that the Food and Drug Administration's (FDA) approval process for new drugs and biologics has on innovation in the discovery and development of new treatments for disease. I am also pleased to present a set of policy recommendations related to the FDA approval process that will help bring a new generation of breakthrough therapies to patients and will help sustain and grow the essential ecosystem that has established the U.S. as the global leader in life sciences innovation.

Venture capital provides the essential fuel for medical innovation, by funding the discovery and development of novel therapies to treat disease. In order to develop new drugs, innovative companies require many hundreds of millions of dollars in capital over a period of many years or even decades. For the past three decades, venture capital has been a primary source of this vital risk capital, has funded the

development of an entire generation of important new medicines, and has financed and helped build almost every successful company in the world-leading U.S. biotechnology industry.

Today, however, the U.S. medical innovation ecosystem is facing severe strains. The cost, time, and risk of developing novel therapies for important diseases have all grown to the point where, increasingly, investors can no longer earn returns on these investments. As a result, the vital risk capital that for the past several decades has funded U.S. medical innovation is being diverted to other industries and other countries. At a time when medical research is exploding with potential, many promising scientific discoveries are not being developed into new treatments for disease due to lack of investment capital.

While many factors have contributed to the escalating cost, time, and risk of new drug development, a changing regulatory environment at the FDA is the most significant. In the late 1980s and early 1990s, patient groups highlighted delays in getting new medicines to patients and pushed for more rapid access. In response, Congress and the FDA worked together to shape a new drug approval system designed to balance the goal of ensuring drug safety with the desire to speed new therapies to seriously ill patients. Throughout the 1990s and through the first part of the last decade, the FDA generally struck this benefit-risk balance effectively and maintained an efficient, predictable review process. This balanced regulatory environment helped bring a generation of vital new treatments to patients in need and helped establish the U.S. as the world leader in life sciences innovation, fostering the rapid growth of a vibrant biotechnology industry and creating more than a million high-quality U.S. jobs.

By the middle of the last decade, however, the political backdrop and public consensus that made all of this possible had changed dramatically. Following the emergence of safety issues with Vioxx in 2004 and other similar high-profile developments, the public discourse about drug regulation began to heavily emphasize drug safety. Far from being congratulated for speeding new treatments to sick patients or for advancing medical innovation, the FDA has instead come under increasingly heavy criticism for failing to do enough to ensure patient safety. Naturally, FDA officials have responded to this changing environment and have shifted to a more cautious, risk-averse posture in the new drug approval process, emphasizing the potential risks of new treatments more than their potential benefits to patients.

Without question, protecting patients from harmful drugs is an essential element of what the public expects from the FDA. But so too is enabling the timely development and availability of new therapies for those in need. Finding the right balance between these important objectives is the central challenge of the new drug approval process.

As a long-standing investor in the development of innovative new therapies, I want to emphasize that the way this balance is struck, by regulators and by policymakers, has tremendously important implications for the health of the U.S. medical innovation ecosystem. The FDA's shift in recent years to an increasingly cautious, risk-averse posture toward new drug approvals has had the unintended consequence of reducing investment in life sciences innovation due to the significant additional time, cost, and uncertainty it has added to the drug development process.

I am especially pleased to have the opportunity to testify today, because I believe the problems are fixable. Twenty years ago, U.S. policymakers and the FDA rose to the challenge and implemented policy solutions that genuinely benefited patients as well as the innovation ecosystem. We have the opportunity to do the same today. I offer a set of specific policy recommendations designed to give FDA the tools and resources it needs to rebalance the new drug approval process in a way that continues to ensure the safety of new products, but also reflects the great benefits of new therapies as well as the immense value of a vibrant U.S. medical innovation ecosystem.

Venture Capital Fuels Medical Innovation

Over the last several decades, venture capital has provided the fuel for U.S. medical innovation. Venture capital has played a central role in creating, financing, and building an entire generation of new companies that have been at the heart of the discovery and development of almost all of the new biotechnology drugs and medical devices of the last 30 years. Venture-backed companies have delivered breakthrough treatments to patients with cancer, diabetes, HIV, multiple sclerosis, orphan diseases, and many other serious conditions. These investments are not only driving innovation; they are also helping to create jobs and grow the economy. In 2010, venture capital-founded and -developed life sciences companies employed more than 1.7 million people in the United States.¹

Venture-backed biotechnology companies are small, emerging growth companies that require continuing investment of risk capital. In fact, more than 90 percent of all biotechnology companies employ fewer than 100 people.² These companies are central to the U.S. medical innovation ecosystem, but they are small businesses whose ability to survive and innovate can be impacted by seemingly minor regulatory factors that increase the cost, time, and risk required to develop new products.

¹ IHS Global Insight 2011

² BIO Emerging Companies Section Membership Survey, 2011.

A Challenging Environment for Medical Innovation

Currently, America's medical innovation ecosystem is under intense strain. At a time when scientific research is generating unprecedented opportunities for breakthrough therapies that improve treatment while bringing down healthcare costs, the venture capital dollars that have been the vital fuel of U.S. innovation are fleeing the life sciences sector and even leaving the country. Fewer new drugs are being developed and making it to the marketplace, and those that do succeed take longer and cost more than in the past. Today, it requires an average of 10 to 15 years and \$800 million to over \$1 billion to develop a new drug, and not only is that cost increasing, but it is increasing at an accelerating rate.^{3 4 5 6} As a result, fewer biotechnology ventures than ever before provide favorable returns to their investors, and venture investors in life sciences struggle to raise funds to create and nurture the next generation of innovative companies.

While other measures of investment are bouncing back from the difficult economic environment, life sciences venture investment is declining. Increasingly, limited partners (the endowments and pension funds and other institutions that provide the capital for venture funds to invest) are telling the National Venture Capital Association that they are reducing or even eliminating the share of investment that they allocate to life sciences venture capital. As a result, a number of the most established venture firms dedicated to life sciences have been unable to raise new funds and have had to reduce or even cease operations. Many other venture capital partnerships are being forced to reduce or abandon life sciences investing, and instead focus on other areas such as information technology, social networking, and, more than ever before, emerging markets such as China.

The following statistics illustrate the depth of the problem facing U.S. life sciences venture capital and the medical innovation ecosystem that it supports:

- During 2010 and 2011 to date, first-time fundings of life sciences ventures – a key leading indicator of the health of the innovation ecosystem – have decreased by more than 50 percent compared to prior years.⁷

³ Returns to R&D on New Drug Introductions in the 1980s," *Journal of Health Economics* 13, no. 4 (1994): 383–406

⁴ H.G. Grabowski, J. Vernon, and J.A. DiMasi, "Returns on Research and Development for 1990s New Drug Introductions," *Pharmacoeconomics* 20, supp. 3 (2002): 11–29

⁵ J. Dimasi and H Grabowski J "The Cost of Biopharmaceutical R&D: is Biotech Different?" *Managerial and Decision Economics* no 28 (2007): 469–79

⁶ Munos, Bernard. "Lessons from 60 years of pharmaceutical innovation." *Nature Reviews Drug Discovery* 8, 959-968 (December 2009).

⁷ BioAdvance, MedTRACK Venture Finance Database

- The total amount of capital raised by venture capital funds decreased by 25 percent in 2010 compared to 2009, representing the third consecutive year of decline.⁸
- The share of venture capital invested in biotechnology declined from 18 percent in 2009 to 12 percent in 2010, the lowest level since 2001.⁹
- From 2008 to 2010, venture investment in U.S. life sciences companies declined by \$2 billion.¹⁰

FDA's New Drug Approval Decisions Have Adversely Impacted Innovation

A strong FDA that makes scientifically rigorous decisions is an essential element of the medical innovation ecosystem. For many decades, the FDA has been the world's highest-performing and most scientifically advanced regulatory body. While other countries have steadily improved their regulatory capabilities, they have done so largely by emulating the FDA, and the world continues to look to the FDA for leadership in regulatory science. Nevertheless, when asked what is the biggest factor driving the increased cost, time, and risk of drug development, almost every venture capital investor and drug developer points, without hesitation, to the way FDA approval requirements have changed over the past decade.

Ultimately, decisions about when and whether to approve new drugs are not just scientific judgments, but also value judgments. All drugs present risks as well as benefits to patients. Rigorous science helps to identify and measure the benefits and the risks, but the question of how to balance the benefits versus the risks, and the question of how much uncertainty to accept when releasing a new product to the market, is inherently a value judgment.

On this score, while the FDA continues to bring great scientific rigor to its decision-making, the last decade has witnessed a major shift in the nature of the value judgments the FDA is making. Compared to a decade ago, the FDA of today is on the whole more risk-averse, and tends to emphasize the risks of new products more than their benefits to patients. This leads the Agency to demand more and more data – larger trials, longer follow-up, and greater statistical certainty about efficacy and safety – before being willing to approve a new product.

This evolution in the value judgments being made by the FDA has not happened in isolation. Rather, it reflects the tenor of the public discourse about the benefits and risks of new therapies. In the late 1980s

⁸ Ernst & Young. Beyond Borders. Global Biotechnology Report. 2011

⁹ Ernst & Young. Beyond Borders. Global Biotechnology Report. 2011

¹⁰ PricewaterhouseCoopers/National Venture Capital Association Money Tree Report: Thompson Reuters.

and early 1990s, patient organizations argued passionately that patients with deadly diseases value new therapies and are willing to accept some risk and uncertainty in exchange for rapid access. At the same time, many observers highlighted the existence of a “drug lag,” noting that novel drugs were generally reaching the market faster in Europe than in the U.S.¹¹ Congress and the FDA responded, implementing a number of forward-thinking regulatory initiatives – including the Accelerated Approval Pathway, Fast Track designation, Priority Review, and regulatory performance metrics and goals – designed to streamline the approval process and speed new drugs to patients. Throughout the 1990s and into the first half of the last decade, the FDA’s decision-making about new drug approvals reflected this broader societal consensus about the benefits of new therapies as well as the importance of safety and rigorous scientific evaluation.

However, the political and public backdrop has changed markedly in recent years. Ever since Vioxx was pulled from the market in 2004, the public discourse about the FDA – reflected in Congress and amplified by the media – has been less about the promise of new drugs, and more about their risks. The FDA has been increasingly criticized for not doing enough to ensure safety, and for taking too much risk in approving new products. Rarely over the past decade has one heard FDA officials being congratulated for speeding new therapies to patients in need or for encouraging innovation. Not surprisingly, the FDA has responded to this environment, shifting to a more cautious decision-making posture, and requiring more and more data to provide a higher degree of statistical proof of both efficacy and safety, before allowing new drugs to market.

While it is undeniably important to assure the safety of new drugs coming to market, it is equally important to recognize the benefits of new therapies. It is also essential to recognize that the way in which these objectives are balanced has enormous implications for our country’s ability to maintain leadership in turning science into breakthrough products. As the FDA becomes more cautious, demands more and more data, and emphasizes the risks of new products over their benefits, the cost, time, and risk of investment in medical innovation all go up, driving investment capital away from U.S. life sciences and into other industries and other countries.

While this is surely an unintended consequence of a cautious, risk-averse regulatory environment, its impact is very real. Notably, the FDA approved an average of 36 new drugs and biologics per year from

¹¹ CHI. BCG. February, 2011. Competitiveness and Regulation: The FDA and the Future of America’s Biomedical Industry

1996 to 2004, but an average of only 21 per year from 2005 to 2010.¹² The most recent data for 2011 to date show the FDA on pace to approve more new drugs and biologics this year than in recent years.¹³ This is certainly welcome news, but there is little evidence yet of a sustained change in the underlying issue, which is the way the Agency balances the benefits versus the risks of new therapies. Investment in the development of novel therapeutics is being impacted as well. Total R&D investment by the U.S. biotechnology industry is down an alarming 27 percent from \$30 billion in 2007 to \$22 billion in 2010.¹⁴

Investing in Novel Therapies is Increasingly Challenging

The shift in new drug approval standards directly impacts the calculus of investors when deciding whether or not to make the high-risk, long-term investments needed to develop new therapies. As an investor in innovative life sciences companies for the past 15 years, I now find it increasingly difficult to make the math work for investment in novel therapeutic product development. I am certainly not alone in this. This is an experience that is widely shared and frequently discussed among venture capitalists and other life sciences investors. Simply stated, promising scientific breakthroughs – ones that a decade ago would have readily secured ample venture capital investment – now languish for lack of investment.

In recent years, along with other life sciences investors, I have watched the calculus for investment turn markedly less favorable in one disease category after another. This has been happening across a wide range of different therapeutic areas. Here, I will briefly highlight three areas – diabetes, obesity and rare diseases – where the investment calculus has been adversely impacted by an increasingly risk-averse posture at the FDA. In each case, my aim here is not to second-guess the FDA's scientific judgments nor its decisions about any specific product. Rather, it is to illustrate the profound impact that these decisions can have on investment in development of innovative new therapies.

Diabetes. Type 2 diabetes is among the largest and most rapidly growing serious health conditions in the U.S., and is a significant driver of increasing healthcare costs. However, due to new FDA requirements, it has recently become a very difficult area in which to invest. In a 2008 guidance document, the FDA notified sponsors of new type 2 diabetes drugs that they will now be required to conduct additional large, long-term safety studies in advance of approval, on top of what were already stringent requirements. While the FDA's goal of more tightly defining the cardiovascular risk profile of new diabetes drugs is clearly a worthy one, this new approval requirement has had major unintended consequences. Due to the

¹² Ernst & Young. Beyond Borders. Global Biotechnology Report. 2011

¹³ FDA, NMEs approved, 2011.

¹⁴ Ernst & Young. Beyond Borders. Global Biotechnology Report. 2011

requirement, the development of a new diabetes drug today costs as much as several hundred million dollars more than in the past, and takes as much as several years longer. This additional burden in time and cost has significantly reduced investment in diabetes drug development. The impact has been especially crippling for the kinds of small, venture-backed companies which have been so critical to the life sciences innovation ecosystem. Just within the past few years, as a result of these new FDA approval hurdles, several venture-backed companies with promising diabetes therapies have been forced out of business, and many others have abandoned diabetes and shifted focus to other areas.

Obesity. Like diabetes, obesity is recognized as a major public health challenge and a key driver of escalating healthcare costs. Over the past decade, venture capital-backed companies took up the challenge of advancing novel obesity therapies to the market. During the past year, however, the FDA denied three consecutive applications for approval of new obesity drugs. One of those drugs, developed by a small company financed with venture capital, was rejected despite an Advisory Committee vote recommending approval. According to the public statements of the sponsor, the FDA is requesting a pre-market cardiovascular safety study that will require between 60,000 and 100,000 patients – a study which would be cost-prohibitive and, for all practical purposes, impossible to conduct. Investors will be unable to justify further investment in obesity therapeutics in the face of requirements such as this.

Rare Diseases. While the FDA's pre-market safety requirements have shaken the innovation ecosystem in areas such as diabetes and obesity, the Agency's escalating requirements for statistical proof of efficacy have taken a toll on the calculus for investment in innovation in many other disease areas. Rare diseases are a case in point.

By definition, the smaller the number of patients affected by a disease, the more difficult it is to enroll any given number into clinical trials. Yet increasingly, the FDA has held treatments for serious orphan diseases to the same level of statistical proof of efficacy as is required for non-orphan diseases. In general, the FDA requires two randomized controlled clinical trials demonstrating a statistically significant and clinically meaningful benefit as the basis for new drug approval. This is an entirely reasonable standard in most situations. However, when applied inflexibly, it drives innovation capital away from certain areas, such as rare diseases, where the small numbers of patients make it difficult and often impossible to enroll multiple clinical trials large enough to meet the traditional definition of statistical significance.

A recent example is Firazyr, a novel treatment for hereditary angioedema (“HAE”), a rare but very serious condition. Firazyr was originally developed by a small venture capital-backed company, which conducted two randomized controlled studies in support of approval. The results of both studies appeared to suggest a benefit for Firazyr, but one of the two studies fell short of meeting the conventional definition of statistical significance. In 2008, citing the need for additional evidence of efficacy, the FDA denied the sponsor’s application for approval of Firazyr.

At the same time, however, the European Medicines Agency (“EMA”) approved Firazyr for marketing in the EU. In contrast to today’s FDA, the EMA has proven to be less wedded to the requirement for two statistically significant randomized controlled studies. While that remains the usual standard in the EU as in the U.S., the EMA is empowered to employ a “weight of evidence” approach, evaluating all available evidence, and interpreting that evidence in the context of the disease and the unmet need, in order to determine whether the benefit of a new therapy outweighs its risks.¹⁵ This “weight of evidence” approach to EU approval decisions, in contrast to the more statistically rigid principles generally applied by the FDA, has profound implications and is a major reason that many observers increasingly consider the EU regulatory environment to be more conducive to life sciences innovation than the U.S.¹⁶

The FDA’s rejection of Firazyr in 2008 is one of a number of FDA actions that have forced investors to reassess the economics of investing in rare diseases. The FDA’s decision on Firazyr jolted investors not only because it came on the very same day that EU regulators decided to approve Firazyr, but also because it appeared to reflect a different balance from what the FDA itself might have struck a decade ago, when regulatory principles were applied in a more flexible manner that aligned with the unique challenges of developing drugs for rare conditions.¹⁷

Over the years, my firm has made a series of significant investments in a variety of orphan diseases, and I am proud to have played a part in the successful development and commercialization of a number of drugs for rare diseases where no prior therapy existed. Unfortunately, as a direct result of the evolution of FDA approval requirements over the past decade, my firm has in recent years been forced to decide against making investments in several potential breakthrough therapies for rare diseases, where 10 years ago, we would have jumped at these opportunities.

¹⁵ Module 5 of Part I of Annex I to Directive 2001/83/EC

¹⁶ CHI. BCG. February, 2011. Competitiveness and Regulation: The FDA and the Future of America’s Biomedical Industry

¹⁷ “Icatibant: Mixed bag for US & EU approval.” Credit Suisse, 25 April 2008.

Cancer Innovation Is at a Crossroads

Over the past two decades, cancer has attracted far more investment capital than any other disease, and potential breakthrough anti-cancer medicines in the pipeline today vastly outnumber those for other therapeutic areas.¹⁸ While many factors have helped create this situation, a central element has been the FDA's approach to approval of new cancer drugs – an approach that has historically struck an effective balance between the benefits and risks of new cancer treatments. However, since late 2009, the FDA has initiated what appears to be a fundamental re-evaluation of the standards for approval of new cancer therapies. The resulting uncertainty has chilled investors' enthusiasm for oncology, as investors fear that the FDA's decision-making in oncology may already be in the process of veering toward the same risk-averse, cautious approach that has impacted other disease areas.

In 1992, with patient groups pushing for earlier access and a public discourse that valued the benefits of new treatments for patients, the FDA implemented the Accelerated Approval pathway, which was designed to allow for earlier approval of new drugs that provide benefit over existing therapies for serious and life-threatening diseases, based on “surrogate endpoints” that are deemed “reasonably likely to predict clinical benefit.”¹⁹ In effect, rather than having to wait for definitive statistical proof that a drug extends patients' survival, the FDA could make the drug available to seriously ill patients in the market based on a more limited package of data, with a commitment from the sponsor to conduct further post-market studies to more completely document the patient benefits.

The Accelerated Approval pathway has been a great success story. While its applicability has been limited only to certain disease areas and certain situations, the pathway has stimulated an explosion of investment in innovation in those diseases, most notably HIV/AIDS and cancer, and has brought immense benefit to patients. In HIV/AIDS, for example, there are now over 20 new medicines on the market. In oncology, the FDA has granted Accelerated Approval to 49 new indications for 37 novel oncology drug products since 1995.²⁰

While recent studies have suggested that innovative medical devices are increasingly reaching the market years earlier in the EU compared to the U.S. and that FDA review times for new drugs may be beginning

¹⁸ Ernst & Young. Beyond Borders. Global Biotechnology Report. 2011

¹⁹ 21 C.F.R. § 314.500; 21 C.F.R. § 601.40

²⁰ Dr. Paul Kluetz. ODAC. February 8, 2011, the U.S. Food and Drug Administration (FDA) Oncologic Drugs Advisory Committee (ODAC))

to lag behind those of the EU regulators,^{21 22} the U.S. has continued to lead the world in cancer drug approvals. A study released last month by Friends of Cancer Research (“FOCR”) found that during the period from 2003 to 2010, more new cancer medicines were approved in the U.S. than in Europe, and new cancer drugs typically became available to patients earlier in the U.S. than in Europe.²³ These welcome results reflect the success of the Accelerated Approval pathway in oncology, along with the willingness of the FDA through most of the decade to take a balanced approach to the assessment of benefit versus risk in cancer drug approvals. Notably, of the 32 novel cancer drugs approved by the FDA from 2003 to 2010, 14 obtained Accelerated Approval, of which 11 were based on single-arm studies without a control group.²⁴

However, an active debate is underway today about approval standards for cancer drugs, and there is serious concern among investors and oncology drug developers that the FDA may be moving away from the balanced approach to oncology of the past two decades and toward the same kind of cautious, risk-averse mindset that has impacted FDA approval decision-making in other disease areas. In particular, recent actions and public statements from the FDA’s Office of Oncology Drug Products have introduced significant uncertainty over how the FDA intends to apply the Accelerated Approval pathway in the future. For example, at an Oncology Drugs Advisory Committee (“ODAC”) meeting in February 2011 and other recent settings, the FDA has raised fundamental questions about the range of situations in which single-arm studies (i.e., studies without a randomized control group, typically using tumor response rate as primary endpoint) and studies using measures of disease progression (such as Progression Free Survival) as primary endpoint should be sufficient to support Accelerated Approval for cancer drugs. During this same time period, companies developing oncology drugs have increasingly reported that in their interactions with the FDA, the Agency has begun demanding overall survival studies in situations where single-arm studies or progression-free survival studies would in the past have supported approval.

While no new formal guidance has been issued on these topics, the uncertainty about the FDA’s direction has cast an alarming shadow over the cancer drug innovation ecosystem and has chilled investment in innovative cancer therapies. The reason for this becomes apparent when one realizes that of the 47

²¹ Josh Makower, “FDA Impact on U.S. Medical Technology Innovation, A survey of over 200 medical technology companies, November 2010. <http://www.medicaldevices.org/node/846>

²² CHI. BCG. February, 2011. Competitiveness and Regulation: The FDA and the Future of America’s Biomedical Industry

²³ Samantha A. Roberts, Jeff D. Allen and Ellen V. Sigal Despite Criticism Of The FDA Review Process, New Cancer Drugs Reach Patients Sooner In The United States Than In Europe *Health Affairs* (2011)

²⁴ Johnson, John R., et. al. “Accelerated Approval of Oncology Products: The Food and Drug Administration Experience.” *JNCI*, Vol. 103, Issue 8. 20 April 2011.

Accelerated Approvals granted to cancer drugs since 1992, 44 have been based on either single-arm studies using tumor response rate as primary endpoint, or randomized studies using measures of disease progression or tumor response as primary endpoint.²⁵ In short, these endpoints and trial designs have been the basis of essentially *all* of the oncology innovation that has been encouraged and facilitated by the Accelerated Approval pathway over the past two decades. Indeed, many of the most important new cancer drugs of the past 20 years – including Gleevec, Alimta, Velcade, Erbitux, and many others – owe their approvals, at least in part, to the Accelerated Approval pathway and to these trial designs and endpoints.

Thus, while it is appropriate for the experts to review and debate the merits of these endpoints and designs, it is essential that this discussion reflect the practical realities of oncology drug development and the incentives for investment in innovation. It must be remembered that the Accelerated Approval pathway has stimulated an explosion of investment in innovative cancer drugs over the last 20 years precisely because it reduced the cost, time, and risk of investment required to get a new cancer drug to market. While randomized studies measuring overall survival are clearly the gold standard in terms of scientific certainty, the Accelerated Approval pathway, and the trial designs and endpoints that have made the Accelerated Approval pathway work in oncology, are essential to the oncology innovation ecosystem.

This debate over cancer drug approval standards is happening as we speak. In light of the unique status of cancer – its devastating impact for patients, its position as the most heavily invested area of drug development, and the explosive pace of basic scientific progress in understanding its mechanisms – the stakes of this debate for the future of U.S. leadership in medical innovation could not be higher.

Policy Recommendations

As I have described, the fundamental challenge facing the U.S. innovation ecosystem for new drugs and biologics is the way in which the FDA balances the benefits versus the risks of new therapies.

Fortunately, this problem is eminently fixable. The FDA remains the most scientifically rigorous regulatory agency in the world, and has demonstrated its commitment to continuously improving its processes and scientific foundation. It has also proven over the past two decades that it has a great ability to adapt and respond to intelligent policy and to the values of the public. Therefore, I offer the following policy recommendations designed to rebalance the benefit-risk assessment in the new drug approval process and to help jumpstart the U.S. medical innovation ecosystem.

²⁵ Johnson, John R., et. al. “Accelerated Approval of Oncology Products: The Food and Drug Administration Experience.” JNCI, Vol. 103, Issue 8. 20 April 2011.

Strengthen FDA's Mission Statement

The FDA's statutory mission should reflect the centrality of its role in the life sciences innovation ecosystem, as well as the degree to which the public values, and benefits from, medical innovation. Currently, the FDA's mission, as stated in the Federal Food, Drug, and Cosmetic Act, is to "promote and protect the public health."²⁶ Congress should update the FDA's mission statement to explicitly reflect that the advancement of medical innovation is one of several core aspect of the FDA's undertaking and is essential to the public health. Such an updated mission statement would provide the basis for the Agency to routinely assess the consequences of its decisions, policies and priorities on unmet medical needs and medical innovation, and would serve as a powerful reminder to FDA staff and to all stakeholders that the FDA's actions and decisions have enormous impact on the life sciences innovation ecosystem.

Expand the Accelerated Approval Pathway into a Progressive Approval System

Congress should expand the highly successful Accelerated Approval pathway into a Progressive Approval system for new drugs and biologics that offer a significant advance in the treatment of serious or life-threatening diseases. While the Accelerated Approval pathway has given the FDA the ability to speed certain products to market based on "surrogate endpoints," the Progressive Approval system should build on the success of Accelerated Approval by addressing the overall benefit-risk balance directly, rather than just the question of endpoints. The FDA should be empowered to grant Progressive Approval at the earliest possible point in development, as soon as the available evidence suggests that a new therapy is more likely than not to provide benefits to patients that exceed its risks. As with the Accelerated Approval pathway, sponsors would be required to conduct post-marketing studies designed to further elucidate the benefit-risk balance, and the FDA would be able to rescind a drug's Progressive Approval status if the available evidence comes to suggest that the benefit-risk balance is unfavorable. Importantly, the implementation of a Progressive Approval pathway would make explicit that the FDA has the authority and the public mandate to behave flexibly, without a "one-size-fits-all" standard of evidence, in approving breakthrough drugs in the context of unmet medical needs.

Empower FDA to Incorporate All Available Evidence in Assessing Benefit versus Risk

Under the Federal Food, Drug, and Cosmetic Act, the FDA is directed to approve a new drug or biologic when "substantial evidence" exists that it is safe and effective when used as intended. Except in certain limited circumstances (such as the Accelerated Approval of new oncology drugs), the FDA has generally interpreted this language to require at least two randomized controlled clinical studies meeting the

²⁶ Federal Food, Drug, and Cosmetic Act, Section 1003.

conventional definition of statistical significance. As illustrated above in the context of treatments for rare diseases, this requirement at times fails to reflect the realities of drug development and lacks flexibility in situations such as orphan conditions, drugs that address major unmet needs in serious and life-threatening diseases, and drugs that present minimal safety risk to patients.

Congress should clarify the standard to make explicit that the FDA is empowered to use a “weight-of-evidence” approach to the assessment of benefit versus risk, taking into account the full context of the disease, the patients being treated, and the nature of evidence available. While placebo-controlled studies with statistically significant outcomes would clearly remain the gold standard form of evidence, this proposal would further empower the FDA to apply rigorous scientific judgment in a flexible manner, in line with circumstances. The weight of evidence approach has worked for the new drug approval process in Europe and for the FDA itself, when it is necessary and appropriate to make decisions without the benefit of statistically significant, randomized controlled data.

Make FDA’s Benefit-Risk Assessments Explicit When Refusing Approval of New Products

It is easy for a regulatory agency to fall into the trap of excessive caution, requiring more and more data and certainty rather than being willing to take risk. To be sure, drug safety is of the utmost importance and is central to the FDA’s mission, but so too are the benefits of new drugs to patients and the health of the U.S. innovation ecosystem. The FDA should be required to fully detail its benefit-risk calculus when it decides to deny or delay approval in favor of collecting more data. This would make explicit the basis on which critical decisions are being made, would help ensure that regulators assess the tradeoff between benefit and risk in a manner that reflects the values of patients and the public, and would facilitate investment in innovation by providing enhanced clarity about the standards against which approval of potential new therapies will be measured.

Ensure Adequate Funding for FDA

A vibrant life sciences innovation ecosystem requires a strong, science-oriented FDA. The FDA’s scope of responsibility continues to expand, and the complexity of medical science continues to grow. Congress should ensure that, through the reauthorization of PDUFA and appropriations, the FDA is endowed with the resources it needs to advance the public health, maintain its position at the cutting edge of regulatory science, and promote U.S. leadership in life sciences innovation.

Conclusion

As I have described, the U.S. medical innovation ecosystem is in jeopardy. Life sciences venture capital, which for the past four decades has provided the basic fuel for medical innovation, is experiencing an alarming decline. Without risk capital, breakthrough science cannot be developed into treatments that cure disease, ease suffering, and reduce healthcare costs. The cost, time, and risk involved in developing new drugs and biologics have increased to unsustainable levels. If investors are unable to earn returns investing in the development of innovative new therapies, investor capital will be diverted to other industries and other countries, and many of the small venture capital-backed businesses that have made the U.S. the world leader in life sciences innovation and have created more than a million high-quality jobs in the process, will cease to exist.

While many factors have contributed to driving up the cost, time, and risk of drug development, the regulatory benefit-risk balance is the key. As the FDA has grown more cautious and risk-averse, and has emphasized the dangers of new therapies over their benefits, the innovation ecosystem has suffered. Fortunately, this is a fixable problem. As Congress debates the PDUFA reauthorization, and as policymakers focus on the need to modernize regulations, streamline government, and enhance innovation, a tremendous opportunity exists to reinvigorate and strengthen U.S. leadership in life sciences innovation. Thank you for the opportunity to share my thoughts and proposals with you today.