Statement of

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Before the House of Representatives

Subcommittee on Health

of the

Committee on Energy and Commerce

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Hearing: 21st Century Cures: Examining the Role of Incentives In Advancing Treatments and Cures for Patients

June 11, 2014

Good morning Chairman Pitts, Ranking Member Pallone, and Members of the Committee. It is an honor to be here today and have the opportunity to contribute to this important discussion.

My name is Fred Ledley. I am Director of the Center for Integration of Science and Industry at Bentley University, and Professor of Natural & Applied Sciences as well as Management. I am a physician and a pediatrician, trained at Georgetown, and at Harvard and Boston Children's Hospital.

In the 1970s, I did graduate research at the National Institutes of Health and at the Food and Drug Administration, and worked with David Baltimore at MIT before beginning my own laboratory in the Howard Hughes Medical Institute at the Baylor College of Medicine. My laboratory focused on inherited diseases in children, and, in 1991, my team was one of the first to receive NIH and FDA approval for a clinical trial directed at gene therapy. In 1993, I was a founder of one of the first gene therapy companies, GeneMedicine, where we worked closely with the FDA to bring gene therapies into clinical trials, and completed an IPO in 1994. In 1996, I became President and CEO of a start-up company in the then-emerging area of personalized medicine, Variagenics, which had their IPO in 2000. I am also the inventor on ten US patents. I joined Bentley University in 2005, where my research focuses on accelerating the translation of scientific discoveries to create public value.

I am here today to share my perspectives as a physician and pediatrician, and my experience as an entrepreneur and executive in the biotechnology industry.

If I leave you with one take away message today, it is that the role of incentives should be to promote the discovery and development of 21st century cures based on 21st century science. This innovation requires sustained support for translational science, from the early stages of basic research, through drug discovery and drug development. This innovation also requires

certainty that the pricing of new products will reflect the value brought to the market, as well as incentives for entrepreneurship. Patent rights advance this agenda by protecting the inventor's priority to novel art so that it can be developed and commercialized. Statutory exclusivities granted to older products can inhibit innovation by drawing away time, talent, and resources from the discovery of new cures. I urge the Committee to focus on the mission of advancing 21st century cures with incentives that promote cures based on the science of the 21st century.

Testimony before this committee has already celebrated the tremendous scientific advances of recent decades. Research from our Center for Integration of Science and Industry, however, suggests that the dramatic scientific advances of the molecular biology era are only now being to be translated into products. In fact, most of the medicines coming to market today were discovered using basic science that is 30-40 years old.

Let me give you an example. Monoclonal antibodies are, today, an important class of new medicines with an annual market of >40 billion dollars.. The basic science that enabled discovery and development of these products was published in 1975. It was not until the 1990s, however, that a monoclonal antibody was discovered that would be developed into a successful product, and not until a quarter century after the original publication, that the first product was approved (McNamee and Ledley 2012).

My colleague, Laura McNamee, recently studied the timeline of translational science for the 100 new medicines approved by the FDA since 2010. She found that the basic science that led to the targeted discovery or development of these products occurred, on average, 40 years before these products were approved (McNamee et al., in preparation). Thus, in the second decade of the 21st century, the pharmaceutical pipeline is not providing 21st century cures, but rather cures based on 20th century science.

Over the past 40 years, basic science has advanced at an exponential, or near-exponential, pace, reminiscent of the exponential growth of computers and information technologies. We are all familiar with how the exponential advance of computers has driven down the cost of technology, while also producing dramatic new capabilities. So to, the products of exponentially advancing biomedical and pharmaceutical science have the real potential to drive down the cost of healthcare, while providing dramatically more effective cures. These are the treatments and cures that the public expects from 21st century science.

One reason the pharmaceutical industry is facing a dwindling pipeline and patent cliff is that it has depended for too long on the products of old science, me-too drugs, product line extensions, and the eternal hope of discovering a blockbuster drug (Munos 2009). Other witnesses today are addressing policies and incentives that accelerate the process of developing new medicines. I would like to focus my comments today on incentives that will move the pharmaceutical industry forward from a reliance on old science towards 21st century cures.

Patent rights are essential to promoting innovation. Patents transform nascent scientific discoveries into economic capital that can be monetized through technology transfer, investments in early-stage biotechnology companies, and licensing fees or royalties paid for rights to the invention. Patents also provide inventors with a window of opportunity to develop and commercialize their innovations. Innovation is promoted by efficient and timely patenting of scientific discoveries as well as existing mechanisms for patent term adjustments when there are delays in issuing patents, and patent term restoration when marketing time is lost in product development or regulatory review.

Statutory exclusivity can have the opposite effect. Extended exclusivity for existing drugs or biologics can create incentives for incremental innovation, making companies less likely to

commit resources to translational science; less likely to discover and develop new medicines; less likely to enter into alliances with entrepreneurial biotechnology companies; and less likely to make acquisitions of such companies. Extended exclusivity granted to products that are dormant or late in their exclusive life cycle are particularly problematic, since such policies explicitly favor the products of older science.

Statutory exclusivity can be used effectively to achieve specific social goals. The Best Pharmaceuticals for Children Act provides six months exclusivity to companies that test their products in children, and has been effective in assuring that pharmaceutical products can be used safely in children (Christensen 2012). The Orphan Drug Act, which provides extended exclusivity for products for rare diseases with limited market potential, has successfully promoted development of cures for many diseases (Melnikova 2012). The difference between these statutory extensions, and some that are proposed, is that they explicitly focus on unmet needs for which market forces provide insufficient incentive, and are limited in term.

Even with market incentives, however, the transition to 21st century cures faces an uncertain path that needs to be nurtured with strategic incentives. Let me share an example of particular personal interest; gene therapy. Recent studies demonstrate that gene therapy works, yet thirty years after basic science established the feasibility of gene therapy, there are no products on the market in the US or Europe. One reason for this lag in commercialization of gene therapy is that, while more than $4.2 billion dollars was invested in gene therapy companies between 1988 and 2012, virtually all of this investment was made in companies with immature, early-stage technologies. By the time these technologies matured to the point that they might generate effective products, investment and pharmaceutical interest had waned. In fact, UinQure, which has a product approved in Europe, Glybera, was in liquidation when approval

was granted, and was only able to attract investment, secure a corporate partnership, complete an IPO, and begin building the production facilities after the product was approved (Ledley, McNamee et al. 2013).

The problem for gene therapy, and many other, innovative cures, is that there are no mechanisms for continuous, sustained support of translational science from the first stages of basic research through drug discovery and drug development. There is a role for incentives that engage stakeholders in the long-term success of innovation. Such incentives could include accounting standards that assign value to investments in R&D (Ledley 2013), valuation models that value the intermediate products and stages of innovation (McNamee and Ledley 2013), as well as tax rates and shareholder rights (Lipton 2014) that favor long-term investments.

The reason we are here today is that the treatments and cures that were developed from 20th century science are not good enough; there are critical unmet needs in diseases that remain untreatable and healthcare costs that seem to be out of control. Incremental improvements or new indications for older products will not meet these needs and can be counterproductive to generating new treatments and cures from 21st century science. In closing, I urge the Committee to focus on the mission of advancing 21st century cures with incentives that move the industry forward from the products based on the science of an earlier age.

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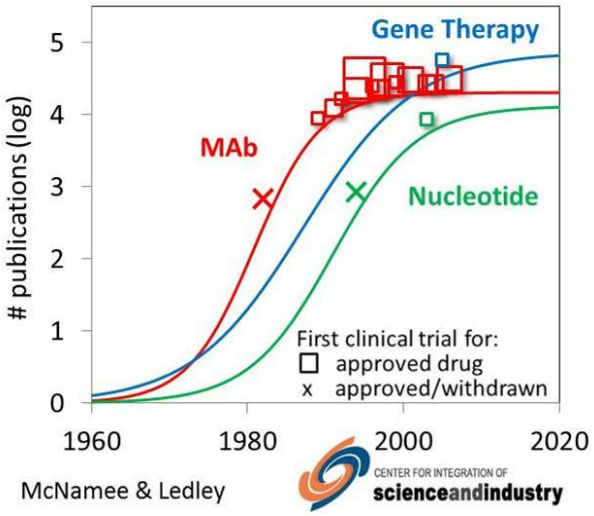
In closing, I would like to thank Chairman Pitts, Ranking Member Pallone, and Members of the Committee for the time to address you today.

NOTES

1. Timeline of monoclonal antibody development (McNamee and Ledley 2012).

The discovery of monoclonal antibody (MAb) technologies in 1975 created enormous optimism that this nascent technology would provide a pipeline of therapeutic products. The early approval of Orthoclone in 1986 reinforced this optimism, but proved to be deceptive. Over the next decade, >200 different MAbs failed in clinical trials, and Orthoclone was eventually withdrawn from the market (Smith 1996). The first successful MAb products were not approved until 1994. By 2012, there were 34 MAb products on the market and >50 in late stage trials (Reichert, Rosensweig et al. 2005; Reichert 2012).



The Technology Innovation Maturation Evaluation (TIME[tm]) model provides an analytical framework for mapping the maturation of technologies. Three biotechnologies (monoclonal antibodies, gene therapy, and nucleotide therapeutics) all exhibit S-curve patterns of maturation similar to those observed in other technology sectors. For all three, products have been successfully launched only as these technologies reach an established stage.

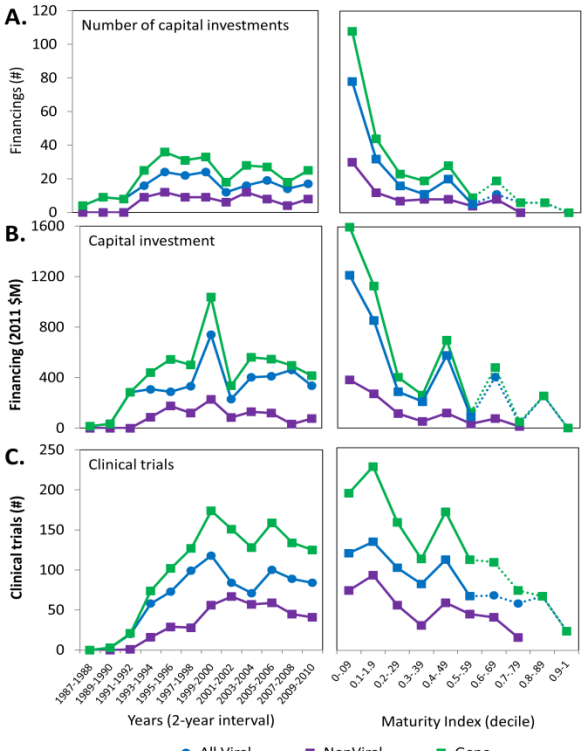
Our analysis of the MAb technology life cycle suggested that the decades of futility in clinical development corresponded to immature stages of the technology life cycle, as the field was grappling with the transition from murine MAbs to chimeric, humanized, and finally human antibodies, while also advancing screening and production methods. Consistent with observations in other technology sectors, MAbs technologies only generated successful products when the enabling technologies reached an established stage (McNamee and Ledley 2012). Since the 2012 publication, the approval of the first gene therapy (Glybera) and the nucleotide therapeutic (Kynamro) similarly correlate with the maturation of these technologies.

2. Why commercialization of gene therapy lagged (Ledley, McNamee et al. 2013)

The prospect of using DNA as a therapeutic, was recognized in the early 1970s (Friedmann and Roblin 1972; Wirth and Yla-Herttuala 2013), and was enabled by the emergence of defective viruses in the early 1980s (Mann, Mulligan et al. 1983). From 1972 to 2012 there were >35,000 research papers on gene therapy, >16,000 US patents issued that reference gene therapy, and gene therapies were investigated in >1800 clinical trials (Alexander, Ali et al. 2007; Alton 2007; Edelstein, Abedi et al. 2007). Recently, there have been a number of dramatic successes in clinical trials for diseases such as hemophilia (Nathwani, Tuddenham et al. 2011), Leber Congenital Amaurosis (Bainbridge, Smith et al. 2008; Maguire, Simonelli et al. 2008; Testa, Maguire et al. 2013), and X-linked Severe Combined Immunodeficiency (Hacein-Bey-Abina, Hauer et al. 2010) that have been heralded as the long-awaited confirmation that gene therapy can be used to safely and effectively treat human disease (Naldini 2009).

As of May 2014, however, there are no commercially available gene therapy products in the US or EU. One product, Glybera, originally developed by Amsterdam Molecular Therapeutics (AMT), received approval from the European Commission in November 2012 (Gruber 2012) after clinical trials demonstrated the safety and efficacy of this product for treating familial lipoprotein lipase deficiency (Buning 2013; Gaudet, Methot et al. 2013). AMT was in liquidation when the product was approved, and unable to launch the product. The company emerged from liquidation in 2013 as UniQure, completed a European marketing alliance with Chiesi, completed a $82M IPO in February 2014, as is currently building production facilities anticipating a launch in 2015.

Our analysis (Ledley, McNamee et al. 2013) used TIME^{TM} metrics to model the maturation of five distinct gene therapy technologies: retrovirus, adenovirus, adeno associated virus, lentivirus, and non-viral. We identified the technology focus of >50 gene therapy companies, and calculated a maturity metric (Maturity Index) for each company's technology at the time of each financing or clinical trial. The results show that over time, the number of capital investments (A, left) and total capital investment (B, left) exhibited a period of growth and then have remained relatively stable to the present time. The same data considered as a function of the Maturity Index, shows that there is a significant negative correlation between maturation and either the number of capital investments (A, right) or total capital investment (B, right). The majority of all investment in gene therapy ($5.3 billion in constant 2011 dollars) has been invested in companies with technologies that have a Maturity Index of <0.3, the level of maturity where successful monoclonal antibodies first entered clinical trials.



Asynchrony between investment and maturation of gene therapy technologies. Left panels show progression of metrics over time, shown for two year intervals. Right panels show the same data as a function of the Maturity Index, shown for deciles. A. Number of capital financings in gene therapy companies. B. Total value of capital investments in gene therapy companies (constant 2011 dollars). C. Number of clinical trials initiated. Note that not all of the ordinal technologies were mature as of the date of this analysis, so points with a Maturity Index >0.5 are shown as dotted lines.

A similar analysis of gene therapy clinical trials shows that while the number of trials has been relatively stable (C, left), a disproportionate number of trials have involved technologies with a low Maturity Index (C, right). This is significant because research in many different technology sectors has shown that early stage technologies commonly do not generate products that can meet the standards of existing markets (Foster 1986; Christensen 1997; Christensen and Raynor 2003).

3. Accounting for R&D as a fixed investment (Ledley 2013).

On July 31, 2013, the BEA announced a comprehensive revision in the calculation of the GDP, which significantly changes the contribution of R&D (BEA 2013). In the new calculation, R&D expenses will be considered a fixed investment and calculated in a new category, termed "intellectual property products." As a result, the calculated contribution of corporate profits and proprietors' income to the GDP will no longer subtract the costs of R&D as an operating expense, but only the industry-specific depreciation of R&D investments as a consumption of fixed capital (CFC). According to the BEA, these changes will provide a "better measure the effects of innovation and intangible assets on the economy."

To an entrepreneur, these changes make sense. The greatest single expense of science-driven, entrepreneurial enterprise is R&D, and the greatest asset of such companies is the intellectual property that results from this investment. In science policy, this is sometimes referred to as "scientific capital." The revised categorization of R&D ascribes a determined value to R&D investments in translational science, and recognizes the "scientific capital" that results from this investment as a positive contribution to the GDP at the time the work is performed.

The principle that R&D represents a fixed investment, as opposed to an operating expense creates a powerful incentive for investment in innovation. Accounting for R&D as an operating expense compromises earnings and profits, and negatively impact a company's near-term valuation as well as its access to capital and its cost. This is exactly the opposite effect that R&D has on long term value creation, where R&D spending may be expected to provide a significantly greater return on investment than ordinary capital. Accounting for R&D investments as a fixed investment would remove an artificial drag on corporate earnings and profits, and enhance the economic incentives for investing in innovation.

4. Valuation of biotechnology companies (McNamee and Ledley 2013)

How is the value of a biotechnology company determined? Earning-based value metrics are not relevant to research-stage companies that operate at a net loss. Moreover, such metrics systematically devalue R&D expenses of revenue-generating companies by decreasing earnings. Present value calculations can ascribe de minimis value to long-term development programs. Accounting standards that define the "fair value" of assets, including intellectual property, are heavily influenced by temporal market conditions. Most financial analysts focus on near-term fluctuations in stock price, which often reflect technical milestones, but not the steady technical progress that enables seminal milestones to be reached.

Gary Pisano (Pisano 2006) has argued that biotechnology is, at its core, a science-based business that requires distinct architecture and business models from other businesses. One critical component of such an architecture is standards for valuing science-based companies that provide for a rational appreciation of value in parallel with a company's technological successes and failures. Investors in early-stage companies should be able to invest in the strategic goals of early-stage companies with the expectation that the company's technical success towards achieving these goals will be reflected in increasing valuations. The fact that such success may not be reflected in economic metrics of value creation constitutes a systematic disincentive for investment and entrepreneurial activity in general. This is evident in the current climate of investment activity, which increasingly eschews investments in translational science, in favor of investments in products whose value can be formally measured by traditional market-based metrics. Mechanisms that credit value to the course of translational science would enable

investors to realize positive returns on investments in effective translational science and ensure that the industry continues to attract the capital required for groundbreaking research and development. For the industry to continue mobilizing the large amounts of capital investment required for translational science, there needs to be greater alignment between milestones of translational progress and measures of the value that can be realized by investors.

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