Financial Incentives to Encourage Development of Therapies That Address Unmet Medical Needs for Nervous System Disorders: Workshop Summary

DETAILS

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FINANCIAL INCENTIVES TO ENCOURAGE DEVELOPMENT OF THERAPIES THAT ADDRESS UNMET MEDICAL NEEDS FOR NERVOUS SYSTEM DISORDERS

WORKSHOP SUMMARY

Sheena M. Posey Norris, Evelyn Strauss, Christopher DeFeo, and Clare Stroud, *Rapporteurs*

Forum on Neuroscience and Nervous System Disorders

Forum on Drug Discovery, Development, and Translation

Board on Health Sciences Policy

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Willing is not enough; we must do."
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This workshop summary has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published workshop summary as sound as possible and to ensure that the workshop summary meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the process. We wish to thank the following individuals for their review of this workshop summary:

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Although the reviewers listed above have provided many constructive comments and suggestions, they did not see the final draft of the workshop summary before its release. The review of this workshop summary was overseen by **BRADFORD GRAY,** Urban Institute. Appointed by the Institute of Medicine, he was responsible for making certain that an independent examination of this workshop summary was

carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this workshop summary rests entirely with the rapporteurs and the institution.

Contents

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Introduction and Overview[1]

Our brains control a vast array of processes that are central to life, health, and identity, but malfunctions in the central nervous system (CNS) instigate a wide range of devastating symptoms. The associated illnesses include developmental, psychiatric, and neurodegenerative illnesses, many of which are chronic and cause serious and long-lasting disabilities. Together, they are extremely prevalent and have an enormous impact from cradle to grave.

These conditions generate great human suffering and impose a tremendous economic load. According to 2014 estimates from the Society for Neuroscience, nearly 100 million Americans suffer from nervous system disorders, and associated annual expenses exceed $760 billion (Choi et al., 2014). Furthermore, falls and road injuries, both of which rank high in causes of disability, can arise from various brain disorders and are not included in the numbers above. Real costs include not only the price of treatments, but also lost productivity of patients and their caregivers. Between 2011 and 2030, mental health conditions will account for 35 percent of projected loss of global economic output from noncommunicable diseases (Bloom et al., 2011).

Several national initiatives have been launched to better understand the brain (e.g., Brain Research through Advancing Innovative Neurotechnologies [BRAIN] Initiative[2]), yet large pharmaceutical companies are divest-

[1]The planning committee's role was limited to planning the workshop, and the workshop summary has been prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants, and are not necessarily endorsed or verified by the Institute of Medicine, and they should not be construed as reflecting any group consensus.

[2]See http://braininitiative.nih.gov (accessed May 8, 2015).

ing from their neuroscience research programs (see, e.g., Pankevich et al., 2014). Despite the tremendous market potential, CNS drugs are relatively unattractive because of perceived high risk**.** The underlying science remains a challenge, and clinical trials can be lengthy and expensive, resulting in high development costs. Furthermore, demonstrating product safety and efficacy in the regulatory review process can be a costly and timely process. These factors, combined with a patent system that rewards treatments with short development times, collude to create a situation that makes it challenging to develop innovative therapies, therapies for chronic or early-stage disease, or preventive therapies—all of which are highly relevant in the world of nervous system disorders. Consequently, many patients have few, if any, treatment options, and drug pipelines in this sector are tightening rather than expanding (Wegener and Rujescu, 2013).

WORKSHOP OBJECTIVES

The Institute of Medicine (IOM) Forum on Neuroscience and Nervous System Disorders, in collaboration with the IOM Forum on Drug Discovery, Development, and Translation, convened a workshop on January 20–21, 2015, to explore policy changes that might increase private-sector investment in research and development (R&D) innovation that fills unmet medical needs for CNS disorders (see Box 1-1 for the Statement of Task). Workshop participants strategized about how to incentivize companies to fortify their CNS drug development programs, shrinking obstacles that currently deter ventures. Representatives from academia, government agencies, patient groups, and industry gathered to share information and viewpoints, and to brainstorm about budget-neutral policy changes that could help widen the pipeline toward drugs that address unmet needs for CNS disorders.

Pull Incentives: Improving Market Protections and Regulatory Processes

This workshop concentrated on "pull" incentives that might maintain and strengthen private-sector investment in CNS R&D innovation by increasing market returns. Many elements were considered, including the importance of patient involvement when weighing the risks and benefits of any possible program. Discussions focused on market protections and regulatory pathways, and the workshop participants tried to strike a balance between theoretical, ideal solutions and those that are slightly ahead

of current practices and thus, likely within reach. Many participants emphasized the need for drugs that have high medical impact, rather than those that are similar to existing agents.

The incentives discussed at the workshop do not require significant public funding. For example, additional market protection for breakthrough drugs that address unmet medical needs, adaptive trial design in which companies have the ability to modify ongoing studies, and conditional regulatory approval of drugs that demonstrate substantial improvements early during clinical development. They are changes that can be implemented through policy and regulatory changes alone. The goal is to improve the risk–benefit calculus so that nervous system drugs will once again compete for the attention of large pharmaceutical companies. Several participants acknowledged that financial risks cannot be reduced to zero, but increasing the reward side of the equation might improve outcomes for people who live with nervous system disorders.

BOX 1-1
Statement of Task

- Examine opportunities and barriers to increasing investments for the development of novel therapeutics to support unmet medical needs for nervous system disorders.
- Explore potential incentives that might lead to a significant reinvestment in research and development (R&D) within the neuroscience sector, while considering the resources needed for implementation. For example,
  - Explore how extending intellectual property (IP) protection and patent life exclusivity might promote R&D.
  - Discuss regulatory changes, such as increased use of intermediate endpoints and conditional approval pathways for therapeutics targeting specific diseases (e.g., Alzheimer's disease, stroke, and schizophrenia).
- Discuss specific considerations for combination therapies and disease-modifying treatments that might require extensive, long-term prevention trials.
- Consider the impact of potential policy changes on patients.
  - Discuss how potential changes in policy may benefit patient outcomes (e.g., access to therapeutics that may delay or prevent the onset of a disorder).
  - Consider the negative implications of such policy changes to patients (e.g., higher out-of-pocket expenses due to the delay of generics).

Push Incentives: Improving the Science

Many factors hinder development of drugs for the nervous system, most of which do not fall under the umbrella of pull incentives. The following section acknowledges some of these factors and directs the reader to previous work in this area by the IOM Forum on Neuroscience and Nervous System Disorders, but is not comprehensive. Although researchers are steadily uncovering disease mechanisms that might suggest new intervention strategies, progress is slow (Pankevich et al., 2014). No amount of economic reward will succeed if the science is not in a position to move forward, said Dennis Choi, professor and chair of the department of neurology, and director of the Neurosciences Institute at Stony Brook University School of Medicine. Identification of molecular targets that are "druggable" has proved challenging, as has validating targets that have nonetheless emerged (IOM, 2013a). Researchers have struggled to uncover biomarkers that can facilitate clinical trials by pinpointing patients who are most likely to benefit from a particular drug or that can serve as endpoints for studies that otherwise would take years or even decades to complete (IOM, 2011). Using animal and other models to understand the human brain poses significant challenges; for example, appropriate animal models do not exist for many human diseases or are difficult to develop, and many aspects of brain biology depend on neuronal networks that cannot be reassembled out of the body (IOM, 2013b).

Numerous groups and institutions are addressing these issues and, despite the impediments, researchers are continuing to expose disease pathways and improve methods for drug discovery and development (Pankevich et al., 2014). To increase efficiency in clinical trials, movements are afoot to create standing clinical trial platforms that are global in nature and that characterize patients the same way, so drugs can be run through the platforms more quickly in Phase II and Phase III trials, said George Vradenburg, chairman and founding board member of USAgainstAlzheimer's, and Janet Woodcock, director of the Center for Drug Evaluation and Research, Food and Drug Administration (FDA). Those drugs that show signs of a positive clinical impact can proceed to Phase III trials, and those that fail have not exhausted large amounts of money. Journals and funding agencies are tackling some of the reproducibility and data-related issues. Although significant challenges are inherent to the field of human neuroscience, the discoveries and technical

advances that will drive drug discovery in this arena are pressing forward and can support innovation (Pankevich et al., 2014).

Recognizing the importance of improving the science in the field to help "de-risk" drug development, several participants emphasized the need for more "push" incentives. "Push incentives are the powerful ones," said Choi, as they de-risk industrial R&D by providing resources that directly promote research in the form of grants, tax credits, or building infrastructure, for example. However, push incentives cost money. Pull incentives, by contrast, increase market returns without requiring up-front financial output. They might complement and enhance the effects of additional investments in research.

ORGANIZATION OF THE REPORT

The following report summarizes many of the presentations and discussions from the workshop. This chapter outlines the motivation for the workshop and provides context. Chapter 2 reviews current market protections and offers possible ways to extend existing legislation. Chapter 3 provides an overview of current regulatory pathways, and the challenges and opportunities in this sector. Chapter 4 describes the critical role of patients in the overarching enterprise of encouraging CNS drug development. It also discusses how patients as well as caregivers would benefit from effective treatments, and it articulates how public–private partnerships, advocacy groups, and health organizations might help advance pull incentives for drug development in neuroscience, several participants said. Although this topic is presented after the concepts related to market protections and regulatory pathways, the benefit to patients and caregivers was the driving force for this workshop, and many participants emphasized that patients need to be engaged in all these discussions from the beginning. Cited references, the workshop agenda, a list of registered attendees, and the participant biographies can be found in the appendixes of this report.

UNMET MEDICAL NEEDS IN NERVOUS SYSTEM DISORDERS

Nervous system disorders impose a heavy weight on society, said Steven Hyman, director of the Stanley Center for Psychiatric Research at

the Broad Institute of Massachusetts Institute of Technology and Harvard University. Brain illnesses are common and often chronic or recurrent. Because the brain controls cognition, emotion, and executive functions such as planning, people whose brains perform suboptimally often cannot do well in school or the workplace. If the condition is severe enough, individuals cannot operate in the home either.

Premature mortality affects economies and so does healthy life lost to disability (Bloom et al., 2011). Brain disorders influence mortality through lethal events such as stroke and suicide, but they exert their greatest effects on disability. Many illnesses strike early, so they can extract huge lifetime tolls. Measuring disability is not easy, said Hyman, in part because it requires comparisons among different symptoms—for example, those associated with psychosis, dementia, paraplegia, and blindness. To address this issue, the concept of disability-adjusted life year (DALY) was developed. DALY is the sum of years lost to premature mortality and years of healthy life lost to disability (US Burden of Disease Collaborators, 2013). In 2010, mental and behavioral disorders accounted for 22.7 percent of all years lived with disability in the United States (Vos et al., 2012).

The prevalence of brain disorders is climbing, in part because the population is aging. Illnesses such as Alzheimer's disease (AD), Parkinson's disease (PD), and other neurodegenerative disorders that disproportionately strike elderly people are on the rise. Hyman translated this fact into expenses associated with dementia: In 2010, the total cost of care purchased in the marketplace was $109 billion; by 2040, it is projected to be $259 billion (Hurd et al., 2013). The aging population is not the only source of the growing weight of nervous system disorders. Rapid urbanization and conflict/post-conflict situations in, for example, Asia, Africa, and the Middle East are increasing the risk of posttraumatic stress disorder (PTSD), depression, and substance use disorders (Lund et al., 2010). The American Psychiatric Association measured general medical care costs of people who have a mental health or substance use disorder and those who do not, said Paul Summergrad, chair of psychiatry at Tufts University and president of the American Psychiatric Association. According to the Milliman and American Psychiatric Association 2014 report, "patients with behavioral health conditions cost an estimated $525 billion in health care expenditures annually" (Melek et al., 2014, p. 20). Insurance data in the United States for 2012 revealed that insured patients with a treated mental health or substance use disorder accounted for more than 30 percent of total health care spending, and on average

had medical costs that were two to three times more than those without a behavioral condition (Melek et al., 2014). This line of reasoning contributes to the economic argument that mitigating these conditions would provide a huge benefit to society.

Furthermore, these diseases carry with them the additional burden of stigma, Summergrad said. This factor adds to psychological suffering associated with them and to their underappreciation and misunderstanding. Summergrad asked two questions: How can the severity of nervous system disorders best be characterized, beyond the science and economic burdens? What is the influence and associated costs of such disorders in other sectors, such as the justice system?

At the moment, many people with CNS disorders are suffering because of the gap between their medical needs and effective treatments, said Hyman. Disease-altering therapies do not exist for neurodegenerative disorders, nor do treatments for the core symptoms of autism or the cognitive aspects of schizophrenia (Pankevich et al., 2014). In addition, contemporary medicines provide little benefit to many people with epilepsy, depression, brain injury, and PTSD, added Hyman.

The Honorable Patrick Kennedy, former U.S. Representative, Rhode Island, co-founder of One Mind, and founder of the Kennedy Forum, said, "At a time when the burden of all brain-related disorders is at an all-time high, when our understanding of the disability and the impact personally on every single family in this country and around the world is profound, it is time that we actually put forward bold ideas to try to make sure that we fix this problem." Resolution of this predicament depends on the development of new treatment and prevention strategies. The market for such therapies is huge, he added.

Why the Corporate Retreat from Neuroscience R&D?

Despite this opportunity to address the current and growing need, industry is disinvesting in brain disorders, especially psychiatric illnesses (Abbott, 2011; Miller, 2010; Stovall, 2011). Six of the 10 largest pharmaceutical companies, based on 2013 global sales, have cut back dramatically in this area (Choi et al., 2014). The number of publicly visible clinical CNS programs in 11 large pharmaceutical companies dropped by 50 percent between 2009 and 2011 (Choi et al., 2014). In addition, venture funding for novel drug R&D (new chemical entities) decreased by 56 percent for psychiatry and 39 percent for neurology in two 5-year periods (2004–2008 versus 2009–2013), compared to a less than 5 percent

decline for oncology (Thomas and Wessel, 2015). Historically, large companies have played an especially important role in optimizing lead molecules and thus turning them into drugs; these outfits have also led in funding the large Phase III clinical trials that establish drug safety and efficacy, an essential step in bringing drugs to market. Furthermore, the disinvestment is rippling into academia and start-up companies, and disrupting discovery and development programs there, said Choi. The full impact of this loss will become more apparent in the future, as lack of current research will translate into fewer products in the pipeline, he added.

Not all companies have pulled back, however; many promising ideas are percolating, and concerted national programs are focusing on brain research, so rich prospects in the field seem likely, said Choi. Even now, drug development is feasible, although challenging. More than 1,800 medicines are in development globally for mental health and neurological disorders (PhRMA, 2015). Several pharmaceutical companies are continuing to engage in neuroscience drug development, and venture capital and other seed investors continue to support CNS biotech companies (Korieth, 2014). The departure of large companies, however, could destabilize the enterprise by decreasing potential partnership opportunities and the ability to sell products or the entire start-up venture to bigger drug makers. Such changes might make the area less appealing for investors (Choi et al., 2014). Furthermore, maintaining a well-populated pipeline is crucial for the future, noted several participants.

Overall success rates in pharmaceutical drug development have fallen, and the cost to discover and develop new drugs has reached the range of $1.8 to $3.9 billion (Choi et al., 2014). Even taking these factors into account, Choi noted that companies are withdrawing disproportionately from neuroscience. The main driver of company departures appears to be the perception that the balance between risk and reward is unattractive, he added: The financial uncertainties are insufficient to justify the potentially large markets and significant benefits to society.

This situation reflects in part a relatively low probability that any given agent will achieve medical or financial success, said Choi. Although 8.2 percent of CNS drugs that entered the clinic between 1993 and 2004 gained regulatory approval—similar to the success rate for cardiovascular drugs (8.7 percent), gastrointestinal/metabolic drugs (9.4 percent), and respiratory drugs (9.9 percent)—any difference can point company decision makers in more fruitful directions, especially as approval rates only partly reflect a broader definition of product success (DiMasi et al., 2010). Other elements that are typically associated with

CNS drug development, such as especially long clinical trials and regulatory agency review times, further contribute to the lackluster appeal of this area. The amount of time for clinical trials plus FDA review of CNS drugs approved between 1996 and 2010 averaged 32 months (35 percent) longer than for non-CNS drugs (TCSDD, 2015). Of new compounds approved by FDA between 1999 and 2013, drugs for neurological and psychiatric conditions required a mean review time of 19.3 months, approximately 31 percent longer than the review time of non-CNS approvals (TCSDD, 2015). Analogous times for drugs to treat cardiovascular conditions, immunological/infectious disease, and cancer required 17.7 months, 12.5 months, and 8.1 months, respectively.

These trends stem from the scientific reality that studying nervous system disorders poses challenges, said Hyman, given the current state of knowledge and laboratory tools. For example, new molecular targets are scarce, and their validation tends to be difficult. Current animal models and laboratory assays do not always predict therapeutic efficacy; the human brain is inaccessible to direct study; and robust biomarkers are scarce (IOM, 2013b). Hyman pointed out that current drugs for psychiatric disorders have the same targets as their 1950s' prototypes, except for lithium, which was first used earlier (Hyman, 2013).

Nonetheless, the time is ripe for progress, said both Hyman and Choi. A recent working group of the Advisory Committee to the National Institutes of Health (NIH) Director concluded that we are now at "a moment in the science of the brain where our knowledge base, our new technical capabilities, and our dedicated and coordinated efforts can generate great leaps forward" (NIH, 2013, p. 9). Understanding of brain biology and disease mechanisms is advancing, and large national initiatives are cultivating and coordinating research in this area (e.g., BRAIN Initiative). These ventures promise to open avenues toward future therapeutics. According to several workshop participants, if the CNS drug development enterprise is reinvigorated, it could take advantage of such forthcoming information and put existing knowledge to clinical use.

"We are in the middle of the early stages of a national and international call for investments in brain research," said Choi. "This is not the right time to unplug the effort."

TOPICS HIGHLIGHTED DURING PRESENTATIONS AND DISCUSSIONS

In summary, advances in the neurosciences have placed the field in a position where it is poised to significantly reduce the burden of nervous system disorders. Many workshop participants emphasized that CNS drug development is difficult, but feasible. Although the path forward ultimately lies in enhanced understandings of disease mechanisms, many promising therapeutic approaches have already been identified. Some companies recognize that idea and are staying the course even now. The objective of this workshop was for participants to discuss approaches for incentivizing R&D that will produce therapies that target unmet medical needs and significantly improve lives in the area of CNS diseases by strengthening market protections and regulatory processes. The intent was not to encourage development of drugs whose structures closely resemble existing agents and that act by the same mechanism of action ("me too" drugs), even though these types of medications can benefit patients by reducing drug prices. Throughout the workshop, participants discussed a number of central themes.

Market Protection

- Several participants argued that rebalancing the underlying risk/reward calculus could help keep companies engaged in making CNS drugs. For example, increased market protections might help increase CNS drug investment.
- Enhanced market protections increase drug costs, and therefore, a few participants stated that it will be important to ensure that new therapies are accessible to patients. Otherwise, the financial incentive will not address unmet medical needs.

Regulatory Pathways

- According to many participants, existing regulatory pathways or moderate adjustments to existing pathways could be used more in the CNS arena to decrease development time. Such pathways include priority review, accelerated review, breakthrough therapy designation, and fast-track designation. Harnessing some of these pathways (e.g., accelerated approval, which allows for FDA approval based on surrogate endpoints) might expose pa-

tients to greater risk. In addition, several participants suggested other proposals, such as adaptive trial design and conditional approvals, to get therapies to patients faster than current processes. To address this issue, a few workshop participants emphasized that patients have a critical role in conversations about how to balance uncertainty and potential benefits when considering how and when to use these options.

Patient Benefit and Advocacy

- Several participants noted the importance of involving patients and caregivers early on in discussions about strategies that might increase incentives for CNS drug development.
- According to many participants, developing and using mechanisms to define values for drugs might help inform stakeholders in the pharmaceutical and biotechnology industry decisions about which risks, benefits, and associated costs will be appropriate. Several participants stressed that patients and caregivers can make important contributions in these areas.
- Stakeholders across all sectors (e.g., government, nongovernment organizations [including patient and disease advocacy organizations], and academia) might benefit from collaborating and presenting a unified front to advocate for change, several participants said.

2

Improving Market Protection

Highlights

- Companies consider many elements when deciding whether to pursue a given drug development project, including the likelihood that the drug will work, costs, and projected financial returns (Meeker and Reddy).
- Decision-making paradigms require that companies calculate the relative value of each potential drug, but this process is not straightforward and contains many uncertainties. Drug-related patents are typically filed early during the discovery period, before clinical testing and the regulatory approval process. In addition to long development times, patents could be found invalid if later challenged, all of which may result in little patent protection time when a drug reaches the market (Longman, McLeod, Reddy, and Roin).
- Numerous pieces of legislation have added market protections to compensate for large amounts of clinical trial and regulatory review time or to encourage companies to invest in areas of particular medical interest, such as orphan diseases, antibiotic-resistant bacteria, or pediatric use (Armitage, Engelberg, and others).
- There is a difference between biologics and small molecules in the data exclusivity period afforded to them. Small molecules receive 5 years of data exclusivity, whereas biologics receive 12 years and may have added protection from the competition of biosimilars because of the trade secrecy involved in biologics manufacturing processes (Paul, Rai, and Reddy).

NOTE: These points were made by the individual speakers identified above; they are not intended to reflect a consensus among workshop participants.

Having an understanding of the elements that contribute to the biotechnology and pharmaceutical industry's decision-making processes to pursue a specific therapeutic area is critical to knowing how best to incentivize R&D that addresses unmet medical needs for nervous system disorders. Individual workshop participants explained how lengthy drug development times drain market protections and discussed existing as well as potential legislation that aims to counteract that problem. Many participants also pointed out that uncertainties about markets and changing policies complicate the ability to assign value to drugs.

HOW COMPANIES MAKE DECISIONS

To inform the discussion about what might encourage companies to embrace CNS programs, several speakers outlined how drug pipeline decisions are made. Such determinations are complicated and depending on the vantage point may not seem to conform to strict logic, said Kiran Reddy, senior director of Corporate Strategy at Biogen Idec. Many groups within a company contribute, he added. R&D, for instance, has a large voice in influencing prioritization, and that voice speaks from the science and addresses issues such as whether the drug is likely to work. Corporate finance attempts to rank order possible drug development programs by assigning a value to each one.

Finance departments strive to allocate capital to maximize value to shareholders, said Reddy. From this perspective, future profits must eventually cover research costs. The associated calculations incorporate inflation, so a dollar spent today is worth less in the future, and accordingly future values and anticipated cash inflows are discounted to quantify the value of a drug program today. For 10 to 15 years, cash flows out; then, assuming the product succeeds, cash starts flowing in, but those dollars are worth less. With such strategic thinking, large organizations try to calculate the relative present value of different projects to figure out which ones to pursue.

The basic logic in these calculations incorporates at least 10 factors, said Reddy (see Box 2-1). This list underscores the idea that companies must balance many issues, including technical risk, development time, time to resolve uncertainty about whether a particular drug will work, expense, and possible payout. Furthermore, such assessments are not performed in a vacuum. Multiple possible projects vie for resources, and decision makers must consider the opportunity costs of investing in a

particular type of compound for a particular disorder rather than a different type of compound for a different disorder.

To produce valuation calculations, analysts must make assumptions about these and other items, and such assumptions are debatable, said Reddy. The challenge for workshop participants is how new policy measures might influence decision-making factors to promote neuroscience innovation.

BOX 2-1
Key Factors That Drive Biopharmaceutical Research and Development (R&D) Project Prioritization

1. R&D costs: In neuroscience, these costs are especially high because clinical trials are large and lengthy.
2. Duration of R&D: This translates into time to product launch.
3. Market size
4. Price: The amount of money that is reimbursed by third-party payers.
5. Market penetration and time to peak sales: Net present value calculations give more weight to cash that comes in sooner than to cash that comes in later. Extending the duration of patent life and/or exclusive marketing rights contributes to the estimates, but the speed with which a drug can get to market has the largest impact on current value.
6. Costs of goods, sales, and marketing
7. Tax rates: Tax breaks can have a big impact on decisions; they might occur when a product is launched rather than in early development stages.
8. Duration of exclusivity: This has a particularly large impact on biologic drugs. Many R&D organizations have focused on biologics not only because of scientific tractability, but also because it is difficult to develop a biosimilar agent, so these types of agents are better protected from competition than are small-molecule synthetic agents.
9. Time line to generic erosion: How long is a product protected from competition by generic versions? Such time lines differ between small (synthetic) and large (biological) molecules. Reddy said that policy changes could bear on this item, particularly by adjusting the so-called risk-stacking effect (further discussed in this chapter).
10. Overall risk adjustment: People's assessment of the relative probability of success for a drug to be approved and to achieve a certain level of peak sales.

SOURCE: Kiran Reddy presentation, January 20, 2015.

David Meeker, president and chief executive officer of Genzyme, said he places unmet medical needs at the beginning of the decision-making paradigm. Company scientists and analysts assess how severe the disease is and what treatment options exist. They take stock of knowledge about the underlying biology, and in particular, whether a reasonable target has been identified and what is known about the natural history, heterogeneity, and other aspects of the disease. Absence of scientific understanding will trump even the most powerful incentives, said Meeker. If a path forward does not present itself, a company cannot proceed, regardless of how rich a possible solution would be if it existed. In addition, effectiveness of the drug needs to be testable, which means, among other things, that patients must be available. Finally, the return on investment is important and relates to the number of patients multiplied by the price. Several participants noted that a crucial component of reimbursement is how much health care systems are willing to pay; regulatory approval alone does not guarantee that third-party payers will cover the drug (see Chapter 3 for more details).

Additional variables contribute to the decision-making process, said Meeker, including the size of the company, how any given project fits into its portfolio, how the particular year is going, and the degree of passion among team members working on the project. Many items factor into choices about whether to pursue a particular area, and algorithms are far from rigid. Ideally, decision makers want to know that the rewards are commensurate with the risks. Meeker added that companies with large and diverse portfolios can be more flexible than those without them. Although incentives are important to the decision-making process, said Meeker, it is hard to know in advance which ones will be important and how influential they will be in any particular situation.

According to Roger Longman, chief executive officer at Real Endpoints, one way to demonstrate and differentiate value is by identifying and measuring all the key elements of medical and economic value. The specific elements will differ among therapeutic areas, but Longman said that they can always be grouped them into three "buckets": clinical efficacy, safety and use (side effects and practicalities of using the drug), and economics (see Figure 2-1). For each competing drug in a specific indication, one must compare performance on the same set of elements, the scores deprived from normalized data on the endpoint underlying the element (e.g., one element of efficacy from Hepatitis C therapy is the endpoint SVR12, whose measurement must be standardized from drug to drug). Moreover, each element needs to be assigned a certain weight de-

pending on its relative importance. Weights can be changed by different stakeholders depending on how they view the element's importance. Once values have been quantified in this transparent manner, they can be compared and the degree of breakthrough value assigned.

A system might be set up in which a patient can then make decisions about whether he or she is willing to pay more for a drug that bestows more value, based on what is important to that individual. Longman believes it is important to standardize definitions of value to enable consumers, physicians, and payers to make informed choices.

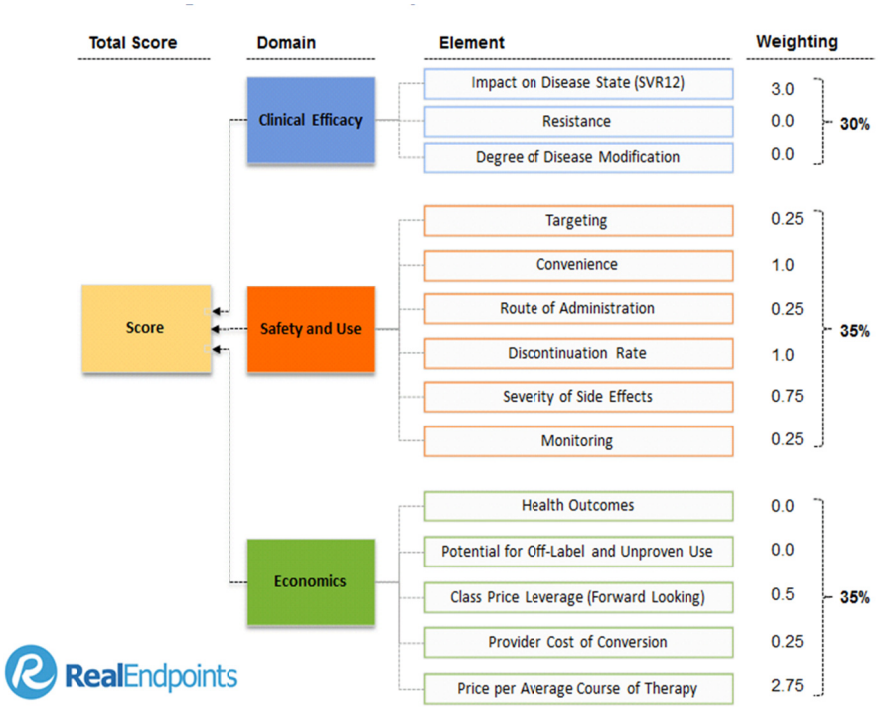

FIGURE 2-1 Elements driving value in hepatitis C drugs.
SOURCE: RxScorecard™ by Real Endpoints LLC; presented by Roger Longman at the IOM workshop on Financial Incentives to Support Unmet Medical Needs for Nervous System Disorders, January 21, 2015.

BUSINESS IMPLICATIONS OF THE STAGNANT R&D CLIMATE FOR CNS DRUGS

Gail Maderis, president and chief executive officer of BayBio, discussed her experience working with the life-science industry in the San Francisco Bay Area. More than 600 start-up companies and several major CNS research institutes reside there, she said, and they have "a wealth of good CNS ideas." These groups, however, cannot find investors to move their product candidates forward. The venture capital community says the CNS sector is "a graveyard littered with clinical trial failures," she said, and when venture capitalists do invest, it's likely to foster the development of a biosimilar agent rather than a novel target or a brand new approach to treating progressive disease.

Start-up enterprises with breakthrough products are told by venture capitalists and pharmaceutical companies that the products look interesting and that the company should come back when it has established clinical proof of concept, said Maderis. A large challenge exists, then, in obtaining funding to reach that stage. She thus made a strong argument for push incentives, but said that pull incentives could influence where investments go. They might increase pharmaceutical investment, although the trickle-down effects to start-ups and academic labs may be small and delayed.

OVERVIEW OF THE CURRENT INTELLECTUAL PROPERTY (IP) ENVIRONMENT FOR THE PRIVATE SECTOR

Patents run for 20 years from the date initially sought, and typically the most important ones are often sought relatively early in the drug discovery process, said Robert Armitage, IP strategy and policy consultant and former senior vice president and general counsel at Eli Lilly and Company. At that point, the patent clock starts, and it continues through all subsequent drug development stages. As a result, preclinical and clinical studies that are necessary to establish key features of the agent's physiological impact, safety, and effectiveness consume potential market protection time.

On average, drugs take 11 to 14 years from discovery to market entry (Paul et al., 2010). That time span grows for treatments that require unusually long clinical trials to demonstrate effectiveness and for preventive therapies, especially those for diseases that manifest over decades. If

FDA approval comes early in patent life, many years might be left, said Armitage; however, if approval comes later, few years will remain. The longer the road to market, the less patent life will be left to protect the discovery once the drug is approved. Armitage noted that the reality is that many medicines end up with no development possibilities because the patent term would be insufficient to make the drug financially tenable. According to several workshop participants, the 20-year patent clock therefore provides systemic bias away from innovative therapies whose development and/or testing is protracted—many CNS diseases fall into this category.

Furthermore, abbreviated regulatory pathways (discussed in Chapter 3) have created an expedited path to market for competing drugs that are deemed *bioequivalent*; such products exploit safety and effectiveness data associated with the original therapy. The weight therefore falls on the drug innovator, not on companies that follow up with similar agents, to gather the information that justifies regulatory approval. With generic drug approval pathways in place, a company can profitably sell generic drugs for little more than manufacturing costs. The company that makes the generic version does not have to find the active agent, develop the drug, or educate physicians on its use, said Armitage. Low-cost production is rewarded rather than innovative product development or tackling a new medical problem. Even the original drug development company has more incentive to develop a minor variation of a current drug—a phenomenon called "evergreening"—than a substantially new agent. The current system therefore has created the perfect way to provide consumers with extremely low-cost medicines, said Armitage, but nothing in patent law ensures that strong protection can be secured for the most promising new or bold ideas.

The patent expiration date typically ends the commercial life of a drug for the company that developed the drug. Unless the patents on a drug are challenged by a generic drug manufacturer, no generic drugs can be approved until the last patent associated with the original one has expired. This is the case even if all safety and effectiveness data have become public.[1] When a patent challenge is initiated, the first generic company that challenges patents can bar FDA approval of all competing generic drugs during a 180-day period after marketing commences for the first generic agent. This incentive encourages patent challenges, said Armitage; consequently, an entire legal industry of patent disputes be-

[1]See the IOM (2015) report on clinical data sharing and the importance of transparency within companies to avoid data secrecy simply to protect IP protection.

tween innovators and companies that make generic products is thriving. The approximate billion dollars per year that industry funnels into such litigations therefore does not go into R&D, Armitage observed (Guha and Salgado, 2013).

Furthermore, the prospect of patent litigation creates inherent uncertainty about whether any given patent will be upheld, said Armitage. Insecurity about the ability to enforce patents disproportionately affects investments in medicines that take the longest time to develop and that are the biggest gambles in terms of prospective success. Both of these characteristics typify therapies for CNS disorders. This so-called risk-stacking effect makes such programs relatively unattractive to pursue. "The best medicines for patients may not always be the medicines with the best patents," said Armitage.

LEGISLATION ESTABLISHING MARKET PROTECTION PERIODS

As previously noted, drug originators are focusing their research on drugs for which they can obtain strong patent protection. According to several participants, compelling bias discourages investigation of treatments for chronic diseases, preventive medicines, or agents that operate by an unprecedented mechanism of action; patent law is not designed to provide the best protection for therapies of these types. Congress has enacted several pieces of legislation intended to counteract some of the negative incentives that the standard patent system offers, particularly in medical areas where drug development is challenging and potentially unattractive.

Hatch-Waxman Act

The Hatch-Waxman Act,[2] formally called the Drug Price Competition and Patent Term Restoration Act of 1984, created the abbreviated FDA approval pathway that made the generic drug industry possible. It barred use of the abbreviated approval pathway for generic drugs until the patents the originator of the new medicine listed in its New Drug Application (the "Orange Book" patents) expired or were successfully challenged. When no patents existed, the filing for generic drug approval

[2]See http://www.gpo.gov/fdsys/pkg/STATUTE-98/pdf/STATUTE-98-Pg1585.pdf (accessed April 21, 2015).

through an abbreviated new drug application route was barred for 5 years. When an originator of a new medicine did secure patent protection, one of the originator's patents could be extended for up to 5 years—but not for more than a total of 14 years after FDA approval. The extension for up to 14 years from the originator's new drug application (NDA) approval date was designed—to partially compensate for large amounts of time spent in clinical trials and regulatory review. According to Armitage, approximately 30 percent of patents that have been extended over the past 30 years have been awarded 14 years of extended patent protection after market entry. Furthermore, if a company is granted a new indication for drug use, a 3-year period is added. Not only does this add market protection for the initial developer, but the Hatch-Waxman Act encourages companies to develop generic versions of drugs. It allows generic small-molecule developers to rely on the innovator's data package after the 5-year data exclusivity period, and when any relevant patents have expired.

Several participants lauded the Hatch-Waxman Act for its positive impact. Nonetheless, they said, it has not fully addressed the problem, as earnings on only 20 percent of marketed drugs exceed development costs (Vernon et al., 2010).

Biologics Price Competition and Innovation Act

As part of the 2010 Patient Protection and Affordable Care Act, Congress created an abbreviated approval pathway for large molecules derived from living cells—biologics—that are "biosimilar" to an FDA-licensed product. This mechanism exists as part of the Biologics Price Competition and Innovation Act (BPCI Act) of 2010,[3] and it affords new biological therapeutic agents 12 years of protection from the date of FDA approval. Six months of market exclusivity are added if pediatric studies are performed. Under the BPCI Act, the number of patents on the reference product does not matter, nor do their expiration dates.

In contrast to conventional medications, which are chemically synthesized and thus whose structures are strictly reproducible and defined, biologics come from living things and are consequently more variable, noted several participants. To qualify for biosimilarity, the product must be highly similar to one that has passed FDA review. Biosimilar products have the same safety and effectiveness profile as the reference product;

[3]See http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Information/UCM216146.pdf (accessed April 21, 2015).

unlike conventionally produced drugs, they are not structurally identical. During the 12 years (or 12.5 years, with the pediatric provision), a competing biosimilar product cannot rely on the safety and effectiveness data that gained approval for the first one.

Arti Rai, professor of law and co-director at Duke Law Center for Innovation Policy, noted that there is nothing magical about 12 years, and it is very difficult to come up with an optimal term. The 12-year decision relied on political realities as well as scholarly work. It takes approximately 13 to 16 years on average for companies to recuperate the costs associated with developing a therapeutic biological agent (Grabowski et al., 2011). Controversy exists about how heavily this item should be weighed when generating a time period for regulatory exclusivity, in part because the goal is not to incentivize the most marginal next drug; the goal is to incentivize drugs that produce the most improvements in quality of life per dollar, said Rai.

Steve Paul, chief executive officer and board member at Voyager Therapeutics, said that the BPCI Act will not create the same price reductions that can be gained by developing small-molecule generic drugs. Rai pointed out that at this time, scientific knowledge and techniques do not support replication of biosimilar agents as quickly and readily as they support replication of small-molecule chemical generic agents.

Orphan Drug Act

The Orphan Drug Act (ODA) of 1983[4] provides an example of legislation that has been a "marvelous success for patients," said Armitage. The act aimed to stimulate corporate interest in rare diseases, which affect fewer than 200,000 Americans. Because of the small patient populations, these illnesses historically had limited market appeal. ODA provides numerous incentives, including tax credits and grants, a fast-track approval pathway, and a 7-year period of market exclusivity for use on the "orphan" condition from the time of FDA approval.

Originally, orphan drugs were for unpatented drugs only, said Armitage. In 1985, orphan drug exclusivity was opened up to patented medicines, and now, the overwhelming majority of orphan drugs have patent protection. When the Hatch-Waxman Act came into being in 1984, it provided more protection for most orphan drugs (particularly new chemical entities) than the 7-year exclusivity period that was pro-

[4]See http://history.nih.gov/research/downloads/PL97-414.pdf (accessed April 21, 2015).

vided by ODA. In the 20-year period that followed the adoption of ODA, more than 400 medications for 447 indications were approved, compared with 10 during the prior decade (PhRMA, 2013).

Best Pharmaceuticals for Children Act

A second example of legislation that has drawn corporate interest toward a particular medical challenge is the Best Pharmaceuticals for Children Act (BPCA) of 2002[5], which was intended to incentivize companies to test drugs that had been approved for adult use in children. BPCA provides 6 months of extra market exclusivity, and it applies to all uses of the medicine, even if its use for children was never approved, said Armitage.

Generating Antibiotic Incentives Now Act

In 2012, Congress passed legislation that might serve as a framework for a type of pull incentive that workshop participants discussed for CNS disorders because it aims to stimulate industry attention on a specific medical field—in this case, drugs that will combat antibiotic-resistant bacteria, said Choi. The Generating Antibiotic Incentives Now Act (GAIN) of 2012[6] attempts to stimulate development in this area, given weak projected market returns. Although the rise of antibiotic-resistant bacteria poses a serious public health threat, the number of individuals who succumb to the illnesses they cause is small, treatment durations are short, and modest pricing and reimbursement is the historic norm, said Choi. Consequently, financial lures tend to be uncompelling (Choi et al., 2014).

GAIN grants an additional 5 years of market exclusivity to new antibiotic agents that qualify (5.5 years if accompanied by a diagnostic test); this period augments the 5-year data protection package provided by the Hatch-Waxman Act or ODA's 7-year registration exclusivity. The act also provides a special regulatory approval pathway. The GAIN Act "is the best example we have yet of a truly therapeutically area-targeted incentive," said Armitage, but it is "too little ventured, too little gained."

[5]See http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/ucm148011.htm (accessed April 21, 2015).

[6]See https://www.congress.gov/bill/112th-congress/house-bill/2182 (accessed April 21, 2015).

POTENTIAL NEW APPROACHES TO EXTENDING MARKET PROTECTION

Focusing on drugs to address unmet medical needs for nervous system disorders, workshop participants explored the idea that increased market protections with data exclusivity might increase R&D innovation by incentivizing industry to advance therapies that require particularly arduous regulatory processes and whose development faces other significant hindrances, such as those previously described.

Europe is ahead of the United States in this area, said Choi. A few years ago, it developed "the so-called 8 plus 2 (plus 1) system of market protection," which provides, to all new drugs after approval, a fixed period (8 years) of data exclusivity plus 2 years of market exclusivity; in addition, it grants an extra year of protection for innovative drugs that provide significant clinical benefits over existing therapies for unmet medical needs (Frias, 2013). "While this is perhaps not exactly what is needed here in the United States," Choi said, "it provides an important conceptual framework."

Increased market protection results in monopolies on particular medicines and associated high costs for patients, according to several participants. It is possible, however, that an individual's need for other types of treatments and care would diminish if the drug worked well. Although patients carry the economic burden of paying for expensive drugs, a few participants stated that society might pay less overall. Effective medicines made available to patients might translate into lower health care costs associated with the disease or even lower justice system expenses. As much as 80 percent of the chronically homeless population have a mental illness, said Andrew Sperling, director of federal legislative advocacy at the National Alliance on Mental Illness. "They are in jails. They are costing this society an enormous amount of money," he added.

21st Century Cures Act

The 21st Century Cures Act, recently drafted by the U.S. House Energy and Commerce Committee, may be a major opportunity to develop incentives for therapeutic development for unmet needs, several participants asserted. The first draft of the bill was released in January 2015,[7]

[7]See http://energycommerce.house.gov/sites/republicans.energycommerce.house.gov/files/114/Analysis/Cures/201-50127-Cures-Discussion-Document.pdf (accessed April 27, 2015).

around the time of this workshop, and it included a section on extended market exclusivity. A second draft of the bill was released in April 2015[8] that has significant changes from the first. While the market exclusivity section has been omitted in the second draft of the bill, the workshop presentations and discussions on this topic may help inform future efforts.

The 21st Century Cures Act aims to "accelerate the discovery, development, and delivery of promising new treatments and cures for patients," and includes several provisions that might help address the challenges that motivated this workshop[9]:

- Encourages repurposing of previously approved drugs, in which patent and market exclusivity have expired, for new indications
- Incorporates patient perspectives into the regulatory process (further discussed in Chapters 3 and 4)
- Streamlines clinical trials
- Modernizes medical product regulation

The market protection section in the original draft of the bill drew upon the Modernizing Our Drugs & Diagnostics Evaluation and Regulatory Network (MODDERN) Cures[10] and Dormant Therapies[11] Acts to allow added marketing exclusivity for a product that is intended to treat an unmet medical need. The bill proposed to guarantee 15 years of market exclusivity for any drug that is approved by FDA for treating an unmet medical need in exchange for relinquishment of the patent rights that companies might have used to extend that term past 15 years, said Benjamin Roin, assistant professor at the Massachusetts Institute of Technology Sloan School of Management. If a drug addressed an unmet need, as indicated by clinical trial results, it would get protection, regardless of whether it is new. Furthermore, the protection would have started not from the patent filing date, but from the date of market entry, he added.

Data and market exclusivity rules are less vulnerable to challenge than are patents, said William Fisher, Wilmer Hale professor of intellec-

[8]See http://energycommerce.house.gov/sites/republicans.energycommerce.house.gov/files/files/114/20150429Discussion-Draft.pdf (accessed April 22, 2015).

[9]See http://energycommerce.house.gov/sites/republicans.energycommerce.house.gov/files/files/f114/FINAL%20Cures-%20Discussion%20Document%20White%20Paper.pdf (accessed April 22, 2015).

[10]See https://www.congress.gov/bill/113th-congress/house-bill/3116 (accessed April 22, 2015).

[11]See https://www.congress.gov/bill/113th-congress/senate-bill/3004 (accessed April 22, 2015).

tual property law and faculty director of the Berkman Center for Internet and Society at Harvard Law School. As a result, the incentive they provide for innovating is less likely to be diluted by the need to pay off generic challengers. For these and other reasons, Fisher said that adjustments in data exclusivity are preferable to adjustments in patent terms.

Defining Unmet Medical Needs

Workshop participants held several discussions on how best to define unmet medical needs. Alfred B. Engelberg, trustee at the Engelberg Foundation, expressed concern that an unmet medical need would be determined and designated not when the drug is approved, but when a company files a clinical plan (discussed further in the Chapter 3). A few participants stated that today's unmet medical need might be resolved 15 years down the road, so companies in the early stage of product development may face this challenge. Marc Boutin, executive vice president and chief operating officer at the National Health Council, said the challenge of circumscribing this benefit has always been an issue. Unmet medical need is defined in the statute, he said, and is based on the definition FDA uses for accelerated approval. Not every product—only about 30 percent of them—qualifies as fulfilling an unmet medical need. A therapy for a condition that is currently untreatable would qualify, as would a product that shows measurable health outcomes and benefits relative to existing products.

Determining Market Exclusivity

According to Armitage, the biggest challenge about the portion of 21st Century Cures that drew from the MODDERN Cures/Dormant Therapies Acts is its fixed market protection—designed to afford parity in market protection for medicines being investigated to address unmet medical needs in life-threatening or other serious diseases, or conditions with medicines that have strong patent protection—of up to 15 years (i.e., the 15-year protection periods serves as both a floor and a ceiling on protection from competition from generic drugs and biosimilar medicine. This section has since been removed in the second draft of the bill. As was mentioned during the discussion about the BPCI Act, data suggest that a typical medicine requires 13 to 16 years to break even, so 15 years is within that window (Grabowski et al., 2011). Numerous participants

shared their thoughts about what an appropriate number (or number range) might be, but no one outlined a clear rationale for any particular length of time. Suggestions ranged between 7 and 20. Multiple speakers indicated that it is difficult to come up with a "good" number. "We know the 7 years is not long enough," said Boutin. "We in the patient community have never taken a position on what is the right period of time. . . . We know that there is a point where it becomes diminishing returns and it prevents innovation. We also know that 7 years is too short. It is clearly somewhere in the middle." George Vradenburg suggested that it might be possible to tier the amount of market protection, based in part on the degree of effectiveness, novelty, ability to treat a previously untreatable condition, or some other performance characteristics. The baseline could be 12 years, and a drug could score additional time if its performance hit specified markers.

A "GAIN PLUS" Proposal for CNS

Choi presented a "GAIN PLUS" proposal for the CNS sector.[12] Based on the GAIN Act of 2010, it would boost market protection for CNS drugs with high medical impact. FDA and its advisers would ensure that this pathway maintains a high bar so that only innovative drugs that address unmet medical needs would qualify, said Choi. Building on the preexisting GAIN legislation would set a precedent for developing a flexible market protection system that can adapt to society's changing needs. In the future, an area other than antibiotics or CNS drugs might become more pressing, and similar legislation could be adopted to encourage activity in that realm, said Choi.

According to Choi, the impact of the GAIN Act is likely to be limited because it does not add to existing market protections. Therefore, it might fall short of the protections that exist under the Hatch-Waxman Act. However, "we think it is the right idea and it is a critical precedent." Choi would like to see the neuroscience version address this key flaw. "We call it GAIN PLUS," he said, "because the extra protections accorded to breakthrough CNS drugs for unmet medical needs are added on top of existing protections, not subsumed within."

Although workshop participants discussed at length whether such a proposal would be feasible, Bonnie Weiss McLeod, partner at Cooley LLP, stated that patent law carries a huge amount of risk. "The law is

[12]For more details on this proposal, see Choi et al., 2014.

changing so fast just with what we have seen with subject matter patentability over the last few years," she said. "Thousands of patents may now be invalid." For example, patent protection for small molecules that were isolated from nature and are used to treat serious diseases is now questionable in light of the U.S. Patent and Trademark Office's implementation of the Myriad Genetics[13] Supreme Court ruling. The current success rate for patent protection (likelihood the patent would be found valid if challenged) is likely around 50 percent, she said. Because the system is struggling to balance rewards for inventors with encouragement of technology development, "I think we are going to see a lot more uncertainty in the patent law before we reach more solid ground," she said.

OPPORTUNITIES TO INCENTIVIZE R&D THROUGH IMPROVED MARKET PROTECTION

- Establish reforms across the biomedical board that ensure a period of market protection, independent of patentability. Toward this end, some participants encouraged the adoption of the MODDERN Cures/Dormant Therapies Acts provisions noted in the first draft of the 21st Century Cures Act, which has since been removed. This provision aimed to encourage companies to pursue drugs that are not under patent protection, but that might prove beneficial in areas of unmet medical needs, regardless of medical area. While several participants were uncertain whether the 15 years is the optimal length of market protection (as noted in the previously mentioned acts), many participants supported the basic idea of having a lengthy automatic term of protection for newly approved drugs that runs from the date of FDA approval and does not hinge on the drug's patentability (Boutin, Fisher, Paul, Roin, Zorn,[14] and others).
- Establish additional market protection for particularly high-impact "breakthrough" drugs in all medical realms—treatments that demonstrate unusually strong clinical and societal benefits in areas of unmet medical needs. Such a system would reward development of drugs that deliver greater impact and might incen-

[13]See http://www.supremecourt.gov/opinions/12pdf/12-398_1b7d.pdf (accessed June 9, 2015).

[14]Stevin Zorn, executive vice president at Lundbeck Research USA, Inc.

tivize truly meaningful innovation (Choi, Fisher, Vradenburg, and others).

- Develop a flexible framework for market protections that can respond dynamically to changing opportunities and society's needs. At the moment, antibiotics and neuroscience drugs rank high by this metric; in the future, other fields might rise in urgency. The infectious disease community has driven passage of the GAIN Act, which provides extra market protection for antibiotics that address unmet medical needs. Conceptually similar legislation could foster growth of the CNS drug development sector. Adding market protections to existing ones (rather than subsuming GAIN-like protections within existing ones) would strengthen such a measure (Choi, Zorn, and others).

3

Strengthening the Regulatory Pathway

Highlights

- FDA has several mechanisms for shortening approval times for therapies that target serious and life-threatening diseases: priority review, accelerated approval, breakthrough therapy, and fast track (Woodcock and others).
- There is a perception that the CNS regulatory environment is fraught with an unusually large degree of uncertainty and difficulty. Further clarity about regulatory processes is needed for pharmaceutical companies to feel secure pursuing drugs in this therapeutic area (Choi, Coetzee, Engelberg, Jonas, Zorn, and others).
- The 21st Century Cures Act, which aims to accelerate the discovery, development, and delivery of new therapies, is currently being discussed in Congress and contains elements that might incentivize companies to pursue CNS drugs that meet serious unmet medical needs (Sperling and others).
- In adaptive trials, drug sponsors can adjust study design based on early data; such trials can save money by focusing on the clinical situations in which the drug is likely to perform best, and therefore might be attractive in the CNS arena (Vrandenburg and others).
- Conditional approval pathways would allow drugs to reach market before the standard information about safety and effectiveness has been collected; additional studies occur after tentative approval, and their results are necessary to gain full approval (Choi, Rogawski, and others).
- Conditional approval pathways could expedite delivery of much-needed drugs and provide companies an earlier return on their investment, but they also pose many challenges in terms of, for example, risk exposure, ensuring that the requisite clinical trials

occur, and the feasibility of rescinding an approval (Kesselheim, London, and others).
- FDA approval does not guarantee that a drug will be reimbursed by third-party payers. Having an understanding early on in the drug development process about what information and data are needed for reimbursement decisions is important (Robinson Beale, Woodcock, and others).

NOTE: These points were made by the individual speakers identified above; they are not intended to reflect a consensus among workshop participants.

Although the regulatory pathway is designed to ensure that only drugs that are safe and efficacious enter the market, several participants noted that the current system has several critical challenges, such as the length of time to approval and to market, and the lack of clarity about regulatory decisions. Workshop participants explored current pathways intended to speed drugs to market in areas of unmet need for serious medical conditions, and examined the promises and pitfalls of adaptive clinical trials and conditional approval pathways for CNS drugs. Many participants underscored the importance of clarity of regulatory processes so industry decision makers can have confidence in making decisions about drug development programs. In addition, an overview of how third-party payers make reimbursement decisions was provided.

DRUG DEVELOPMENT: A REGULATORY VIEWPOINT

Janet Woodcock noted that nervous system disorders cause a vast amount of suffering to patients, family, and society, and there is a tremendous urgency to respond. For FDA, this means doing everything it can to stimulate development of therapeutics. To provide context for an informed discussion about possible policy changes aimed at stimulating innovation in CNS drug discovery, Woodcock described key aspects of the drug development pathway from the regulatory vantage point. Product developers typically require two elements to be in place to pursue a particular drug, she said. First, they need to see a market. In the CNS sector, the market is easy to recognize because disease prevalence and incidence are increasing, and the conditions are common. Second, product developers also need to know that a predictable path to market exists—not

necessarily an easy path, Woodcock said, as some failures are inevitable in the realm of drug development. However, predictability is key.

Predictability is heavily influenced by how much is known about the basic biology of the illness, Woodcock said. For example, to get a clear result about whether the drug works, a clinical trial must be long enough that, without intervention, the disease would have progressed. Along these lines, several participants noted that information about natural history is important because study design must take into account what's known about disease progression relative to the margin of error in measurements and random symptom variability in the population. Some trials are too short to observe a change, even if the drug is effective.

In addition, Woodcock and others highlighted the importance of biomarkers. They can help diagnose a disease and thus identify individuals in whom a potential drug can be tested. Furthermore, biomarkers that reliably predict the amount of time until some particular symptom or event will appear can help inform how long a trial needs to be. The most important type of biomarkers, said Woodcock, are pharmacodynamic ones that reveal early during treatment whether the drug has the desired effect. Because trials need to be long enough to observe a change, surrogate endpoints—such as pharmacodynamic effects—can be useful, especially for diseases that occur over long periods of time. Ideal features, including information about the disease's phenotype, natural history, and pathogenesis, are absent for many nervous system disorders, Woodcock said.

Existing Accelerated Pathways

FDA has several mechanisms that have been designed to encourage and accelerate development and review of drugs that address unmet medical needs in the treatment of serious or life-threatening conditions: priority review designation, accelerated approval, breakthrough therapy designation, and fast-track designation (see Box 3-1). Woodcock illustrated crucial features of these approvals through the lens of Alzheimer's disease. Given that no effective treatments exist for this serious illness, drugs that have nonclinical or clinical data to demonstrate their potential to have a disease-modifying effect to address the unmet need could obtain fast-track designation. To get breakthrough therapy designation, a company would need clinical data that indicate a change in the trajectory of the disease. That is a high bar, but if such evidence existed, FDA would be asking how it can help make the drug, manufacture it, test it, and get it further evaluated, said Woodcock.

BOX 3-1
FDA Accelerated Regulatory Pathways[a]

- **Priority review:** FDA's goal is to act on an application within 6 months (which is shorter by 4 months than the normal review time).[b] During that time, the agency assesses whether clinical data establish that a new therapy advances treatment for a serious and life-threatening illness. To be designated a priority review, the application should contain data suggesting that the agent provides significant improvement in safety or effectiveness compared to existing therapies, not just deliver the same effect, even if the agent itself is new.

- **Accelerated approval:** FDA gives approval based on a surrogate endpoint or intermediate clinical endpoint that is reasonably likely to predict clinical benefit. For some diseases, long periods of time can elapse before an individual feels or functions better; in these situations, the surrogate might change more quickly. The surrogate endpoint allows FDA to approve these drugs faster than it would be able to do if it relied on measurable clinical benefit. In general, the drug should be expected to provide an advantage over existing therapies.

- **Breakthrough therapy:** This designation has been implemented to expedite approval of drugs that promise to deliver a substantial improvement over existing therapy in a serious and life-threatening disease. Preliminary clinical data are needed to suggest this improvement and obtain a designation. Currently, 23 compounds are approved in this category (FDA, 2015). In each case, preclinical data suggest that the agent could be a game changer in the relevant disease.

- **Fast track:** This designation is designed to facilitate development and review of drugs intended to fill an unmet medical need for a serious condition. Preliminary nonclinical or clinical data are needed to suggest the drug's potential. The designation confers a variety of benefits, which might include more frequent meetings and/or written communications with FDA to discuss the drug's development plan, including collection of appropriate data needed to support drug approval, design of clinical trials, and use of biomarkers. Fast-track designation does not lower approval standards.

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[a]http://www.fda.gov/forpatients/approvals/fast/default.htm (accessed April 22, 2015).

[b]http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf (accessed April 22, 2015).

SOURCE: Presented by Janet Woodcock at the IOM Workshop on Financial Incentives to Support Unmet Medical Needs for Nervous System Disorders, January 20, 2015.

For priority review, the data in the application would show there is a significant advance in safety or effectiveness over existing therapies. Finally, for accelerated approval, FDA would have to see the effect of the drug on a surrogate or on an intermediate clinical endpoint. For example, FDA has issued draft guidance for developing drugs for the treatment of early-stage AD that says it would use accelerated approval for a drug that improves neurocognitive testing in pre-symptomatic patients (FDA, 2013). If a battery of tests established delay in decline of neurocognitive testing, FDA would consider accelerated approval for that application, said Woodcock.

In the context of this workshop, said Woodcock, the question is what else might be done beyond the existing pathways. She emphasized that there are trade-offs between lowering standards to get more drugs to people and maintaining high standards, but getting fewer treatments on the market.

REGULATORY CHALLENGES SPECIFIC TO CNS DISORDERS

The investment community views drug development for CNS disorders as "a green field, but with tons of boulders," said Jeffrey Jonas, chief executive officer at SAGE Therapeutics. He pointed out that people are very aware of the large and public failures of CNS trials and how much those failures cost. The feeling is that CNS companies have overstated the efficacy of their molecules, said Jonas. Furthermore, there is a perception that the CNS regulatory environment has much more uncertainty than other areas, said Jonas, and that it is especially difficult to obtain approval for drugs that target neurological and psychological ailments.

Aaron Kesselheim, associate professor of medicine at Harvard Medical School and Brigham and Women's Hospital, agreed with Jonas that studying new drugs for certain CNS diseases—particularly chronic ones—can be very difficult because disease courses can be highly variable and there are no validated biomarkers or other surrogate endpoints available. When investigators cannot easily predict which drugs will or will not work, obtaining regulatory approval for those drugs could be

marked with some uncertainty, because current FDA standards require demonstration of substantial evidence of efficacy based on adequate and well-controlled investigations. Kesselheim pointed out that if drug companies did not need to demonstrate efficacy and safety to FDA, the market would be deluged with ineffective or unsafe therapies, as it was in the early part of the twentieth century, before FDA's current standards existed. In addition, he noted that current FDA standards are highly flexible with regard to medications that address unmet medical needs such as those that are innovative or that treat life-threatening conditions. In those cases, FDA often accepts earlier-stage trials and less certainty about safety or efficacy in approving new drugs.

As discussed in Chapter 1, FDA approval times for CNS disorder drugs exceed those in other disease sectors. Approval rates fall only slightly short of those for other medical areas, but this minor difference combined with the other difficulties associated with drug development in the neurological realm makes the area relatively unappealing, said Dennis Choi.

Although the pathways that Woodcock described are available for drug development across all realms, said Jonas and Steven Hyman, barriers exist to using them in the world of CNS disorders. The current state of knowledge limits use of existing mechanisms intended to facilitate drug assessment in the CNS arena, said Hyman. For example, the accelerated approval pathway depends on the existence of a suitable biomarker, and such surrogates for clinical endpoints are not available for many nervous system disorders, he added. For some conditions, delaying time to progression might provide a measurable endpoint, said Gail Maderis, but in the area of neurological diseases, that endpoint usually requires long and large trials.

Currently 88 biologics and drugs have breakthrough therapy designations (FDA, 2015). Only four of these compounds are in CNS, said Jonas. Furthermore, available evidence suggests that there is a bias away from small innovators. Of the 26 public disclosures from November 2013, 16 of the drugs that were given breakthrough designations for 2013 were from large pharmaceutical companies (Mullard, 2013). Some of the features that make a condition/drug combination amenable to study are not accessible to small companies. Large entities sometimes have data from other projects in their portfolio that can provide knowledge that helps them explore new ideas and/or design strong trials, said Jonas. Furthermore, they are more likely to have the financial resources to gather other valuable information, such as performing a natural history study.

Such capability can open up exploration of a rare and understudied disorder or a disorder for which registries do not exist or give substandard quality data. Jonas concluded that some of the regulatory initiatives may not benefit small-company innovators, especially in CNS, where datasets are often incomplete.

Jonas provided an account of an individual with Lennox-Gastaut syndrome[1] who was in an intensive care unit in super-refractory status epilepticus.[2] No conventional interventions were helping. With no approved treatments, the family and treatment team were faced with withdrawal of care. This individual then had a dramatic response to an experimental drug, getting better and going home. Jonas asked workshop participants to think about what happens in this context, where innovation exists, but an approved therapy does not. It is not easy to see how a conventional clinical trial could be conducted. Furthermore, statistical analysis in such situations poses a challenge because it is unclear how many patient responses constitute statistical significance. The ability to get accelerated approval on findings that are biologically plausible should trump statistical purity in such disease settings, said Jonas. Woodcock said FDA does accept compelling series in which no one expected people to rise from their bed and walk, yet they did.

FDA needs to maintain flexibility, asserted Timothy Coetzee, chief advocacy, services, and research officer at the National Multiple Sclerosis Society. Twelve disease-modifying therapies have been approved for multiple sclerosis (MS), and this situation has started "locking in the regulatory process and expectations," said Coetzee (NMSS, 2015). When a new approach comes along, one must prove that the alternate strategy should be accepted, he said. The MS community is currently grappling with this issue in the area of progressive stage of the disease, as clinical trials that test drugs for this condition will be substantially different from those for the relapsing–remitting form. Regulators should think about new outcome measures "that perhaps haven't been qualified," he said. "This is where I think the advocacy community and others are going to have to come in and say, 'this is where patient risk/benefit decision making needs to be weighed.'"

[1]A severe form of epilepsy.

[2]Persisting and potentially life-threatening seizure activity despite anticonvulsant treatment.

POTENTIAL MECHANISMS TO ADDRESS REGULATORY CHALLENGES

Adaptive Trial Design

Given the complexity of drug discovery and development for CNS drugs, measures are being proposed to adjust the approval process to better address the realities of these illnesses, according to several participants. For example, a portion of the 21st Century Cures Act, which is currently under discussion, has grown out of acknowledgment that existing trial design and analysis might not be a good match for all disorders (USHOR, 2015a,b). A few participants noted that drug sponsors might want to test products in early disease stages, before well-established clinical endpoints have appeared. In this situation, which applies to many CNS disorders, several participants noted that adaptive trial designs might be appropriate, as they allow companies to modify ongoing studies. FDA, however, has not incorporated these types of trials into its routine approval process. The 21st Century Cures Act proposes to permit adaptive trial design and associated analytic methods, a strategy that might better fit some CNS trials, according to a few participants.

Adaptive clinical trials allow changes in study design in response to analysis of data at pre-specified points, noted George Vrandenburg. They leverage early data to guide decisions that can accelerate time lines and reduce costs by focusing the trial on the most promising doses, disease indications, and patient populations (FDA, 2010). Such a mechanism would afford companies the flexibility to adjust trials if early results reveal that a particular subpopulation of patients responds differently to a drug, for instance. A few participants noted that this pathway could save money and speed the discovery of significant clinical findings. The caveat is that such trials might produce data that confound interpretation.

Conditional Approvals

The topic of conditional approvals arose in several contexts during the workshop.

Through this proposed mechanism, a drug would be approved on the basis of information that suggests it is reasonably safe. Clinicians would then test the drug in different patients and attempt to identify what characteristics best predict a positive response, said Michael Rogawski, professor of neurology and member of the Center for Neuroscience at the

University of California, Davis. With this information, companies could design and perform properly powered and controlled clinical trials—and they could identify subsets of patients for whom the drugs will be most helpful.

Woodcock said that the main conceptual problems with that strategy is that it is not always easy to figure out why certain people respond, and identifying the predictive characteristics can be extremely difficult. Also, approving a drug based on safety data gleaned from Phase I and Phase II studies would only guarantee that the medicine does not cause a large number of people to have a "dramatic event," she said. Detecting subtle increases in dangerous side effects requires large study populations. In addition, Woodcock stated that at this time FDA does not have statutory approval to issue conditional approvals for human drugs.

Kesselheim said that identifying subsets of people who respond to a given drug would be beneficial, but given the current state of knowledge about how to conduct rigorous studies in pharmacoepidemiology, can only be done in a reliable way in a clinically controlled environment. If results from a trial comprised of a large, relatively nonselected group turns out negative, but a responsive subpopulation emerges, such post-hoc subgroup analyses should lead to subsequent prospective trials testing that specific subgroup. Kesselheim pointed out that all biostatisticians would agree that post-hoc subgroup analyses are simply hypothesis-generating exercises. He therefore cautioned against approving drugs shown not to work in their clinical trials merely on the basis of supposedly positive effects in post-hoc subgroup analyses before those hypotheses can be further evaluated. Kesselheim added that FDA approval of a medicine for which efficacy has not been demonstrated would be problematic for many other reasons. For example, FDA's stamp of approval is psychologically powerful, and will give physicians and patients the sense that it will work before there were robust data about the agent's efficacy. It also complicates the conduct of subsequent clinical trials because a patient would have the choice of receiving a drug FDA-approved for his or her condition through normal channels or being put in a trial with the potential prospect of not receiving the drug; predictably, fewer patients would choose the latter option. A few participants noted that the proposed conditional approval system would rely on the fact that the therapy is not yet well validated, and therefore, has not received full endorsement. The thought is to have a mechanism in which a drug is brought forward in a conditional, preliminary fashion—with appropriate restrictions. This mechanism in turn might increase FDA and

payer leverages on reaching a conventional standard of approval, countered Choi. Woodcock asked how FDA would restrict distribution of the drug and determine who should have access to it. What are the implications if the drug is later rescinded?

Reducing Time to Market

Choi proposed one version of a conditional approval pathway for CNS drugs that might stimulate development in this area by reducing time to market (Choi et al., 2014; Eichler et al., 2012). In this system, highly selected drugs would be marketed in a limited fashion, based on biomarker or intermediate clinical data; a full period of market protection would become available after the drug sponsor obtains conventional data and clears the usual regulatory hurdles. So far, such a pathway has applied primarily to HIV/AIDS and cancer drugs, but it could be expanded to include a broader range of highly selected CNS therapies, said Choi. This mechanism entails added risk to patients, as it would reduce time in clinical trials before approval, and thus, less safety and efficacy data would be collected before approval. Given that the quality of surrogate markers in neuroscience is generally not as strong as those in HIV/AIDS and oncology, patient involvement would be crucial for making decisions about the appropriate risk/benefit spectrum for any particular drug combination, he added. In addition, several participants noted that input would be needed about providing acceptable cost to patients and payers.

Post-Approval Data Collection and Retroactive Approval

This and other ideas engendered more discussion on the topic of post-approval data collection, retroactive approval, and associated issues. Robert Armitage expressed concern about using retroactive approval measurements to determine periods of market protection, compared to a conditional approach conducted earlier on in drug development based on biomarkers, because doing so would increase uncertainty about the patent litigation. Companies would not know whether they would receive extra regulatory protection at the time when they have to decide whether to pursue any given project. The decision would be made after the product is on the market, by which time the development work is done. Furthermore, Armitage added, the political and economic environment might differ from when the decision was made, which would exacerbate the uncertainty. Hyman reinforced this idea; part of the challenge with

such a system, he said, is providing predictability. It forces companies to take risks before FDA approval, knowing they will have to demonstrate utility after a drug hits the market.

Adding to skepticism about the feasibility of this approach, Kesselheim said that FDA has limited authority to require post-approval testing and then to withdraw a drug if it does not meet the specified goals. Numerous studies show that manufacturers' post-approval trial commitments to the FDA can be delayed or not completed. Bevacizumab (Avastin), for example, was approved based on a surrogate endpoint for metastatic breast cancer. When more convincing clinical studies showed that the drug actually did not improve survival for this condition and was associated with important safety issues, it took nearly 1 year of appeals and hearing to remove the indication. A few participants, however, endorsed some form of ex post facto approval. William Fisher, for instance, discussed the idea of using post-marketing data to determine whether a particular drug should receive "breakthrough" status.

Ethical Considerations

Alex John London, professor of philosophy and director of the Center for Ethics and Policy at Carnegie Mellon University, discussed ethical issues associated with reducing time to market. Given that companies derive great benefit from passing this milestone quickly, and many patients with serious illnesses who do not currently have useful drugs are willing to try therapies that have not been fully evaluated in clinical trials, stakeholder interests seem to align. There are, however, "trade-offs and pitfalls that come from trying to compress this time line," he said. Early-phase studies provide crucial information about how best to use the drug—the clinical window for intervention, appropriate indications and dosage, and under what conditions toxicities appear. To shorten the time period of pre-market testing, it is likely that clinical trials would accept a more idealized and narrow population for study; as a result, some of this information would not be forthcoming before approval.

In principle, these data could be gathered after market entry, but the clinical environment is "noisier" than the trial environment, said London. Small effects are harder to detect, and doing so takes longer. Patients and third-party payers will bear this burden. "You have a trade-off," he said. "Should you learn some of this information in smaller populations in controlled studies early on or if you rush to market, are you going to

have to learn that information later in less controlled settings where you expose larger numbers of patients to burdens?"

In addition, post-marketing studies suffer from another hazard, said London. People might hesitate to participate in studies because they could receive a placebo or the standard drug rather than the new one. "If you increase market access early, are you going to deplete the population of people who would be willing to participate in the studies that we need in order to ascertain whether these things have genuine efficacy?" he asked. "If you do that, then you have effectively closed the door" on attempts to gather crucial clinical data.

What might be more efficient for the developer could be less efficient for patients as a whole or for third-party payers. "There are issues about fairness and shifting these costs, offloading these costs onto other parties with the explicit goal of trying to increase the time to profit for one of the most profitable industries in the world," said London. Furthermore, although patients might be willing to accept increased risk, serious adverse events can have a chilling effect on development. They also can sow distrust in innovative companies and regulators. Coetzee underscored the idea that workshop participants held widely disparate views on whether and how to improve the regulatory process. He noted a "mixed kind of view" about whether such changes are needed and highlighted the strong "differences of perspective."

CLARITY OF REGULATORY PROCESSES AND DECISIONS

Woodcock emphasized the importance of predictability, as previously discussed, and described the agency's efforts to communicate and work with relevant constituencies on the use of the various existing regulatory pathways. Regulatory transparency is important for companies to have a clear understanding of the development process and what is required, said many workshop participants. For example, many participants said it is crucial that terms and standards used by FDA are clearly defined and that better communication between FDA and investigators is needed regarding available pathways that are underutilized by the CNS community.

Definitions of terms such as "unmet medical need" and "breakthrough" are not explicit, and this situation creates problems, said Engelberg. Marc Boutin emphasized that the MODDERN Cures Act defines "unmet

medical need" based on what FDA uses for accelerated approval. Lengthy discussions were held among the group that crafted the legislation and people at NIH and FDA to devise the "right definition," he said. The resulting language has been used by FDA for decades; the agency understands how to use it to good effect. Boutin gave some examples: A therapy for a condition without a treatment would qualify, as would a product that improves on an existing product with regard to measurable health outcomes and benefits. "There is a lot that goes into it, but FDA is skilled and practiced at defining what this is," he said. The common impression that "every product would qualify for FDA's definition of an unmet medical need" is misguided, he said. In the MODDERN Cures Act, "unmet medical need" is determined and designated not at the time a drug is approved, but at the time a drug sponsor files a clinical plan, said Engelberg. This can be problematic because companies tend to be overly optimistic; they often think that agents that are the second or third in a class will meet some unmet medical need. Perhaps those medications will work for longer than existing ones or eliminate a side effect, but those types of unmet medical needs lie on a different plane than a therapy for a serious disease that is currently untreatable. Engelberg said the only time anyone can reasonably assess whether a drug meets an unmet medical need is when it is approved; even then, that designation should be given only if the approval process contains a standardized way to compare effectiveness with existing treatments.

Engelberg also said a much stronger definition of "breakthrough" is needed to ensure that only the real value-added drugs are eligible. Fisher discussed possible ways to determine whether a drug should be categorized as "breakthrough":

- Assembly of expert panels to predict whether a particular drug will be a breakthrough. This strategy likely would not appeal to innovators because they would have to expose themselves to such testimony, noted Fisher.
- Pre-approval (ex-ante) demonstration of increased efficacy through clinical trials. This scheme would be more empirically grounded, but it would be expensive and difficult.
- Post-approval (ex-post) demonstration of increased efficacy or social benefit in terms of saved DALYs. This determination would be made years after drug approval, when it is clear how well the drug is performing. At that point, a decision would be made about whether it has demonstrated sufficient breakthrough

status to entitle it to the extension. The advantage of this approach is that a clear indication is obtained of the drug's benefit, and the sponsoring pharmaceutical firm is pressured to adopt pricing and distribution strategies that will maximize the social welfare benefits. If the therapy reaches only a few people, it will not demonstrate huge social gain.

"With respect to what kinds of drugs to incentivize, my suggestion is do not rely on expert panels," said Fisher. Instead, he proposed that such decisions should depend on demonstration of health benefits through clinical trials.

In addition to standardizing and communicating key definitions, other opportunities for improving regulatory transparency exist. Jonas said there is a perception that various FDA divisions take different approaches to novel therapies. This perceived lack of consistency undermines companies' efforts to prepare properly and efficiently for review. Part of the challenge, said Coetzee, is not just to determine what members of the FDA leadership think about the various ideas discussed in the workshop, but also how guidelines are implemented on a day-to-day basis. It will be important to work out details about how the sponsors and agency interact, and about the guidance that FDA provides when sponsors are launching clinical trials and doing other work required for drug development. "I think implementation of these issues is actually just as critical as having a high-level discussion around it," said Coetzee. See Box 3-2 for global development regulatory opportunities.

BOX 3-2
Opportunities for Improving Pathways to Market: A Global Perspective on Dementia

Improving regulatory processes to help bring innovative therapies that treat unmet medical needs for nervous system disorders to patients faster requires a global effort, according to several workshop participants. Using dementia as a starting point, Raj Long, senior regulatory officer for integrated development in global health at The Bill & Melinda Gates Foundation, described the efforts from the G8 Summit on Dementia held in December 2013[a] which brought together health and science ministers from all G8 countries to discuss finding a cure for dementia. The summit resulted in the Declaration and Communique that set out a vision for international collaboration and a series of high-level actions. In addition,

Dr. Dennis Gillings was appointed as the World Dementia Envoy and a World Dementia Council was formed, bringing together a group of experts to advise and fundraise in an international forum. Each country was also charged with hosting a follow-on global dementia legacy event to continue to discuss how to foster the development of effective therapies for dementia.

As a follow-on activity, the first Global Dementia Regulators workshop was held in November 2014 to discuss dementia research gaps, development challenges, and regulatory science. Long noted that the regulatory science draws from the technical science, and the lack of knowledge about the underlying pathophysiology of dementia is a major factor of dementia developmental failures. Regulators from 10 different agencies attended the workshop as well as industry stakeholders, patients, and clinicians to look at dementia with a single lens. The participants identified six initial key areas as potential areas of impact.

1. **Attrition analysis.** Identify research and development (R&D) challenges by analysis of attrition data of dementia development failures in the past 15 years. The initial attrition analysis of the IMS Lifestyle R&D database show that of 250 trials, 76 percent did not have a reason for attribution. The goal is to expand the analysis to three other clinical trial databases (one in the United States, Europe, and the World Health Organization), and through the International Federation of Pharmaceutical Manufacturers and Associations, start conducting focused interviews with industry to capture any missing information that is not clear in the databases.

2. **Clinical trial efficacy.** Integrate lessons from oncology, rheumatoid arthritis, and other therapeutic areas where applicable to dementia clinical trials (e.g., master protocols). This may be particularly helpful for different types of dementia in which separate trials would not have to be done for each subtype.

3. **Multilateral cooperation.** Potential international platform of regulatory agencies to foster opportunities for multilateral dialogue.

4. **Modelling and extrapolation.** Trials in Alzheimer's disease (AD) and dementias challenged by individual variability (symptoms and clinical measures). For example, explore potential for extrapolation models that translate rare genetic forms of dementia to the wider population, based on an empirical model of human disease.

5. **Composite endpoints.** Given that it is challenging to measure and quantify cognitive impairment in early stage AD, develop and accept a common battery of endpoints (e.g., lessons learned from rheumatology).

6. **Risk/benefit analysis.** Write a concept paper to consider how best to balance possible benefit given the high level of uncertainty. Consider ethical, legal, and societal concerns.

[a]https://www.gov.uk/government/publications/g8-dementia-summit-agreements (accessed April 22, 2014).

SOURCE: Presented by Raj Long at the IOM Workshop on Financial Incentives to Support Unmet Medical Needs for Nervous System Disorders, January 20, 2015.

REIMBURSEMENT: THE DECISION-MAKING PROCESS

In addition to transparency about regulatory processes and definitions, several participants sought clarity on reimbursement decisions, for example, knowledge about the size of the eventual marketplace. That number derives in part from the prevalence of conditions that a drug might treat, which directly affects reimbursement decisions. Rhonda Robinson Beale, senior vice president and chief medical officer at Blue Cross of Idaho, discussed how health plans decide what drugs to cover. The amount of money that goes into specialty drugs recently has increased dramatically. In 2012, these agents cost $87 billion, which was 25 percent of the total amount of money spent on drugs and 3.1 percent of the total national health care costs (UnitedHealth Group, 2014). In 2010, specialty drug expenditures amounted to 20 percent of total drug costs (UnitedHealth Group, 2014). Providers are part of the equation, because they are now becoming payers as they create their own insurance plans, said Roger Longman. In these situations, doctors and other health care workers are incentivized to understand the relative benefits of different therapies, including the economic ones. Doctors are no longer thinking only of therapeutic value; they are also thinking of economic value, said Longman.

Coverage choices are made in large part based on rebates: Pharmaceutical companies pay health plans (or whoever is buying the drug) a certain amount, based on usage. In the absence of dramatic, provable

differentiation in the clinic among medicines with the same indication, the importance of finances increases, said Longman. More expensive drugs must, in a cost-constrained economy, prove that they are worth more, noted Longman; otherwise, the cheaper drugs start to look more valuable.

Insurance companies describe the scope of their covered services with the phrase "medical necessity," which relies on demonstrations of comparative effectiveness and generally accepted medical practice, said Robinson Beale. Medically necessary treatments are backed by evidence that is reproducible with fidelity, and the treatment is important for preserving life at a reasonable level of functionality. In other words, every physician who is delivering such services is getting similar outcomes, and the service is not more costly than an alternative service or drug that is equally effective. That kind of information is not easy to get, as clinical trials do not always use the same endpoints or outcome measurements, said Robinson Beale.

Health plans have technology reviews or pharmacy and therapeutic reviews that examine the research. They examine FDA decisions and all the evidence they can find that relates to the effectiveness of pharmaceutical and other technologies, with the goal of determining whether a particular treatment is clearly effective. They also look at explicit practice guidelines, which generally come from subspecialty organizations. Because a typical practice guideline costs more than $350,000, practice guidelines are generally outdated and do not include the latest research, said Robinson Beale. Insurance companies seek guidance from FDA about which patient populations benefit from new treatments, but such an approach does not take into account information gathered by practicing physicians, who commonly use drugs off label as they attempt to improve outcomes for their patients. In addition, Robinson Beale noted that clinical trials do not always compare the test treatment with a standard one, so when a new drug comes to market, insurance companies do not know how it compares with available treatments. She added that long-term and post-clinical trial information is sporadically available, which means that no reliable mechanism exists by which to understand long-term effects of drugs.

From Robinson Beale's point of view, research evidence should clearly identify the specific affected populations based on neurocircuitry aberrancies or biomarkers, not just diagnostic classifications from the *Diagnostic and Statistical Manual of Mental Disorders*. Furthermore, insurance companies need to know what populations have not been test-

ed so they do not pay for an expensive drug for a one-person experiment. Robinson Beale added that she would like to see clear delineation of drug effects, duration of effects, and long-term outcomes, some of which might be established after market with a patient registry process for high-cost drugs or rush-to-market drugs. This way, the payer can continue to learn about how those drugs affect the population. Lastly, evidence reviews from FDA should be practice-guideline ready, she said, meaning they should be explicit enough that a doctor has clear directives about the conditions for which it has been approved and is effective.

OPPORTUNITIES TO INCENTIVIZE R&D BY STRENGTHENING REGULATORY PATHWAYS

- Amid the broader discussion, several participants also made a specific proposal to develop a regulatory pathway that aggressively hastens conditional approval of drugs that help patients with serious CNS diseases for which no therapies exist. Such a pathway would empower FDA to extend the existing accelerated approval pathway to CNS drugs that demonstrate substantial improvements early during clinical development based on biomarker or intermediate clinical data, with the understanding that such surrogates are not as available or strong as they are for other medical arenas in which this type of pathway has previously been deployed (HIV/AIDS and cancer). This pathway would:

    1. Harness the existing accelerated approval pathway to allow FDA to accept surrogate markers of efficacy for drug approval;
    2. Attach to the accelerated approval a set of appropriate, but stringent, restrictions on pricing and use, trying to strike a balance between those items and appropriate protection and financial return for industry sponsors.
    3. Once the drug is released onto the market, drug makers would conduct studies to confirm, refine, and/or adjust knowledge about its clinical utility; after this data collection step—using conventional clinical endpoints—the drug would receive consideration for full approval.

- Given the added risk to patients due to reduced time for accrual of safety and efficacy data before conditional approval, patient

input will be important for informing decisions about appropriate circumstances under which to deploy this pathway. Pilot use of this mechanism would target only a few drugs, which show especially great potential in terms of medical impact, strong scientific support, and the availability of a useful biomarker or intermediate clinical endpoints.

This mechanism is intended to increase market protection for therapies that address medical problems that currently have no effective treatments, and its initial use would be targeted toward a few drugs that show unusual promise in terms of effect on a serious unmet medical need, underlying scientific support, and availability of an appropriate surrogate marker.

Woodcock raised several challenges about this proposed mechanism, stating that there are a number of legal and ethical considerations, including determining which patients should have access to the drug, restricting the distribution of the drug to the limited population, and facing the implications if the drug has to be rescinded (Choi, Engelberg, Maderis, O'Donovan,[3] Reddy, Rogawski, and others).

- Promote adaptive trial designs, which could facilitate companies' ability to focus on the most clinically relevant uses for a given drug or combination of drugs in an efficient and cost-effective manner (Rogawski and Vradenburg).
- Encourage FDA to issue guidelines that improve clarity about numerous aspects of the approval process, such as how drug sponsors can demonstrate eligibility for dormant therapy designation; improve access to FDA staff by allowing drug sponsors of dormant therapy drugs to request meetings that will inform the development of clinical plans that would support drug approval (Zorn).

[3]Mary O'Donovan, executive director of regulatory affairs at BioMarin Pharmaceutical Inc.

4

Patient Benefit and Engagement

Highlights

- Patients and caregivers can provide crucial information about what kind of risks they would be willing to accept in exchange for a possible new therapeutic agent in any given clinical situation (Boutin, Chiarello, and Maderis).
- Value determinations for potential treatments might include consideration about impact on caregivers as well as patients; preventive medicines—including those that delay onset of serious nervous system disorders—can deliver tremendous benefits to patients and caregivers alike (Comas-Herrera).
- Public–private partnerships and advocacy groups could contribute significantly to activities that might bolster pharmaceutical company pursuit of CNS drugs (Boutin, Hyman, Kennedy, and Reddy).

NOTE: These points were made by the individual speakers identified above; they are not intended to reflect a consensus among workshop participants.

Patients know more about their diseases than anyone else and, thus, they have much to offer any conversation about the value of any given drug, weighing risks versus benefits, and other key issues, emphasized several workshop participants. Many factors contribute to a drug's worth, and the relative importance of each one will vary greatly from drug to drug and patient to patient. In addition, participants discussed the unique

opportunities public–private partnerships and advocacy groups have insofar as contributing to the endeavors discussed during this workshop.

PATIENT INVOLVEMENT: UNDERSTANDING RISKS AND BENEFITS

Throughout the workshop, many participants stressed the importance of including patient viewpoints on key discussion points in the drug development process, such as whether to get a drug on the market quickly or take longer to ensure safety, and how to weigh the advantages of increased market protections with the associated disadvantages of delaying availability of less expensive generic agents. Several participants discussed the unique and indispensable input patients can contribute into determining the value of a given treatment. "The notion of benefit–risk . . . has to reflect the end user," said Marc Boutin, who emphasized that patients should be engaged from the very beginning of drug development. "Everyone in this room has a Smartphone," said Boutin. "There is no company—Apple, Samsung, you name it—that would even change the color of that product without consulting the end user first. And yet in drugs and biologics, you do not consult with [patients] until post-market or at best Phase III. We can change that paradigm."

Lauren Chiarello, senior director of federal government relations at the National Multiple Sclerosis Society, said that acceptable risk will differ depending on the illness, an individual's disease trajectory, prognosis, personal choice, and numerous other issues. For example, the particular symptoms a person is encountering "can really dictate your risk/benefit tolerance," she said. Furthermore, reaction to health status can change. A new diagnosis might shock a person, yet later, that same individual might learn how to accept and live with it.

MS currently has 12 disease-modifying therapies; however, none of them can stop or treat the illness (NMSS, 2015). Chiarello pointed out that a few months of approval time are significant for a person who is living in a wheelchair. "I know that a lot of those patients are looking for something similar to an accelerated approval pathway to help shorten this time, should there be a breakthrough for someone whose current therapies are not working," she said. Chiarello gave a fairly recent example of individuals' willingness to assume risk. A drug called Tysabri was put on the market, and 4 months later was removed because it put some people at risk for a condition called progressive multifocal leukoencephalopathy

(PML), which is often fatal. There was an outcry because many MS patients wanted access to this potent drug, one of the most effective compounds on the market, despite its potential drawbacks. For an MS patient, the small risk of a potentially fatal side effect, such as the possibility of developing PML, is balanced against the possibility of 2 years of freedom from a wheelchair and the hope that another new treatment will extend mobility down the road, said Gail Maderis. Patients want to be able to drive their risk decisions, Chiarello said, and have the relevant conversations with their health care providers. The drug has returned to the market and the manufacturers have instituted a risk minimization program for PML.[1]

Legislation Encouraging Patient Involvement

Prescription Drug User Fee Act

Chiarello emphasized the importance of patient involvement for drug development, and noted that the most recent round of Prescription Drug User Fee Act[2] reauthorization called for increased patient participation in the drug review process. She suggested that expanding that enterprise to collect more information about the needs of patients would be beneficial as well. Maderis reinforced and extended this point. We often think of value in terms of the risk/benefit trade-off for patients, she said, and that varies from disease to disease and from patient to patient. For example, a newly diagnosed Alzheimer's disease patient who is faced with the prospect of taking a new treatment with limited clinical data or the possibility that he or she might not recognize an unborn grandchild might opt to take the new treatment. Different people might make different choices in those situations, said Maderis.

21st Century Cures Act

In the latest version of the 21st Century Cures Act, patient involvement in drug development is discussed. Many participants observed that patients understand their illnesses better than anyone else, and the draft legislation proposes that FDA establish a way to incorporate patient ex-

[1]See http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformation for PatientsandProviders/-UCM107197.pdf (accessed April 22, 2015).

[2]See http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM2005475.htm (accessed April 22, 2015).

perience into the regulatory decision-making process. Patients might register their opinions about, for instance, how heavily to weigh potential benefits versus risks associated with new treatments. Individuals (even those who have the same disease) vary in their willingness to accept any particular risk in exchange for any potential benefit. The legislation calls for FDA to deploy a process by which companies submit patient experience data that would be considered during the approval process.

Even with new incentives for developing drugs that address unmet medical needs, several participants stated that novel treatments will only move slowly toward patients unless clinical trial times are shortened. The 21st Century Cures Act attempts to strengthen the ability of companies to harness surrogate markers to assess efficacy in clinical trials. Formally qualifying such endpoints might encourage their use because companies would have more confidence that FDA would accept them during the evaluation process, said several participants, including Stevin Zorn, executive vice president at Lundbeck Research USA, Inc.

Furthermore, a few participants noted that FDA would be authorized under the legislation to approve drugs based on early safety and effectiveness data. Information about the effects of a given treatment continues to amass after FDA approval, and the 21st Century Cures Act attempts to harness that knowledge. It includes mechanisms for companies to communicate, so treatments whose known efficacy expands after initial approval can be used efficiently in new settings. Several participants noted that the idea is to optimize patient care while retaining appropriate safeguards. Then, the agency could hold companies responsible for assessing these features of drug use after it goes on the market. If companies fail to deliver on such post-marketing requirements, FDA could withdraw drugs from the market.

DETERMINING VALUE TO PATIENTS

Value can also be viewed in economic terms by patients—for example, in terms of the ability to keep a job or live life independently without the cost of caregiving services. Although value calculation from the patient perspective is complicated, drug development speed matters, said Maderis. The time to get to new treatments is absolutely crucial. Time equals life or quality of life for people with neurodegenerative diseases, she said. From the payers' standpoint, the situation is equally complicated, said Maderis, and does not necessarily align with the patient view-

point. For many illnesses, prevention or early intervention leads to lower health care costs, so there is inherent value in treating disease early. Most neurodegenerative disorders, however, do not follow that trend, noted several participants. The costs associated with dementia often are not borne by third-party payers, but by family members who provide care (Thraves, 2014). The economic benefits of delaying progression may bestow mainly on the patient or the family. From a broader societal standpoint, the value equation is clearer. New treatments cost the health care system money, but the value in reducing disability payments, increasing gross domestic product, and generating income taxes is significant. The upshot is that time matters for patients and for society.

Delaying Disease Onset Could Save Billions of Dollars

Adelina Comas-Herrera, research fellow at the London School of Economics and Political Science, talked about the importance of measuring the value of drugs before considering whether they deserve preferential treatment in the patent system. Performing this assessment is not necessarily straightforward, and different appraisal schemes might lend themselves to different diseases. To illustrate this point, she used the example of AD.

DALYs do not properly measure the effects of AD for several reasons, noted Comas-Herrera. First, drug trials generally do not measure the impact of the treatment on caregivers (productivity, well-being, etc.), which can have economic implications (see Chapter 1). Furthermore, measuring the quality of life of someone with moderate to severe dementia is difficult. Research has demonstrated that people with severe dementia score higher on quality-of-life outcomes than do people in a moderately impaired state (Hounsome et al., 2011). Comas-Herrera suggested that those afflicted with severe dementia do not seem to care much that their cognition is worsening. They report stable quality of life that varies by degree of depression and anxiety, but not by degree of cognitive function (Hoe et al., 2009). A logical, but problematic, conclusion might be that someone with severe dementia is doing "better" than someone with moderate dementia, said Comas-Herrera. Furthermore, a drug that improves cognition might not improve quality of life, whereas such a drug could significantly reduce the amount of care a person needs. Economists who are trying to evaluate drug benefits have many of the same methodological problems with the information provided by pharmaceutical companies. William Fisher suggested that the solution is to

refine the metrics rather than to abandon the DALYs approach entirely. The challenge, he said, is to better define assessments of quality of life.

Although many uncertainties limit economic forecasts, the care of people with dementia will cost much more in the future than it does today without new therapies, said Comas-Herrera. Dementia is not just an issue for developed countries; it is a global problem (see Figure 4-1). Its prevalence is increasing more quickly in low- and middle-income countries than in high-income countries. The Alzheimer's Society has estimated that dementia costs the United Kingdom £26.3 billion per year ($40.4 billion), £11.6 billion ($17.8 billion) of which is borne by unpaid family caregivers (Prince et al., 2014). The situation is similar in the United States (Hurd et al., 2013). Comas-Herrera discussed a project that models the hypothetical impact on health and social care costs by 2040 of a new treatment for AD (see Box 4-1).

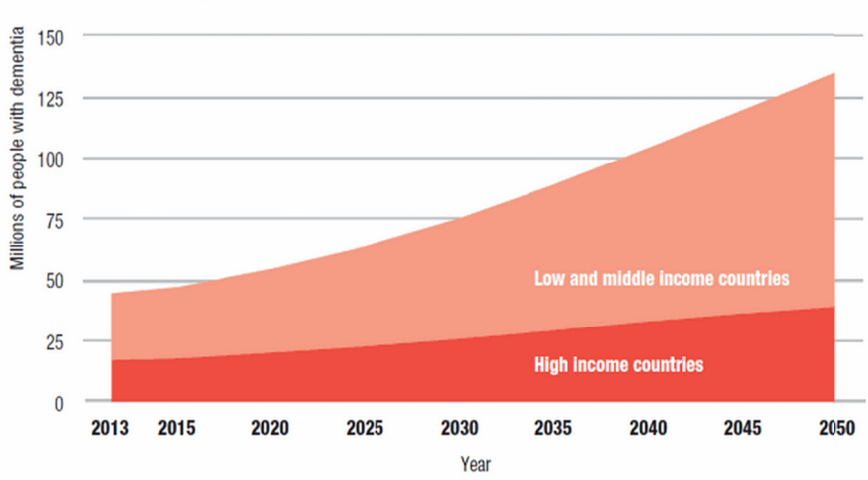

FIGURE 4-1 Number of people with dementia in low- and middle-income countries compared to high-income countries.
SOURCE: Prince et al., 2013; presented by Comas-Herrera at the IOM Workshop on Financial Incentives to Support Unmet Medical Needs for Nervous System Disorders, January 21, 2015.

BOX 4-1
Treating Alzheimer's Disease:
Modeling the Health and Social Costs

As part of the Modelling Outcome and Cost Impacts of Interventions for Dementia (MODEM)[a] project in the United Kingdom, Comas-Herrera discussed a research project that modeled the hypothetical impact on health and social care costs by 2040 of a new treatment for AD. The research team had the following questions:

- How many people with dementia will there be from now to 2040, and what will the costs be of their treatment, care, and support under present arrangements?
- How do costs and outcomes vary with characteristics and circumstances of people with dementia and caregivers?
- How could future costs and outcomes change if evidence-based interventions were more widely implemented?

The exercise assumed the following:

- A new drug becomes available in 2020.
- In 2020, the whole population ages 75 and older is screened (except those already diagnosed) for a biomarker that indicates high risk of developing AD.
- The new drug is prescribed to all those who screen positive (plus those ages 65 to 74 already been diagnosed with the condition).
- Prescription is for the rest of the person's life, and does not replace existing symptomatic AD drugs.

The model tested several scenarios, including some combinations of the following variables: the effects of a treatment that delays onset by 1, 3, or 5 years; slows progression by varying degrees, with and without an increase in life expectancy; and delays onset by 3 years and extends the mild and moderate state by 30 percent, with and without an increase in life expectancy.

According to the analysis, the most expensive scenario arises if people remain in the mild and moderate stages of disease and live longer. Delaying onset of the symptomatic phase delivers the largest reduction to health and social program expenses as well as unpaid-caregiver costs. Drugs that delay the onset of the symptomatic phase therefore would save large amounts of money. If we measure effectiveness only by considering the impact on the person who is ill, Comas-Herrera said, we

miss a huge potential savings of disease-modifying interventions. Including the collateral costs allows one to build a stronger case for the value of early intervention. Many economists are arguing that clinical trials for such diseases should also assess the impact on unpaid caregivers, she said. Clinical trials measure physical and cognitive symptoms, but the impact of dementia is much more complex. Furthermore, people with advanced cognitive deficits incur especially high costs due to comorbidities and hospitalizations (higher risk for falls, urinary tract infections, and respiratory infections compared to people without dementia) (Delavande et al., 2013; Zuliani et al., 2012).

[a]http://www.modem-dementia.org.uk (accessed April 22, 2015).

SOURCE: Presented by Adelina Comas-Herrera at the IOM Workshop on Financial Incentives to Support Unmet Medical Needs for Nervous System Disorders, January 21, 2015.

CREATIVELY ENGAGING PUBLIC–PRIVATE PARTNERSHIPS, ADVOCACY GROUPS, AND NONPROFIT HEALTH ORGANIZATIONS

Public–private partnerships, advocacy groups, and nonprofit health organizations can help foster, enrich, and inform activities aimed at developing pull incentives for drug development in the neurosciences, according to many participants. Such outlets provide a mechanism for facilitating conversations among patients about appropriate trade-offs between potential risks and benefits, and for collecting and communicating relevant information to government agencies.

Similarly, public–private partnerships, advocacy groups, and nonprofit health organizations have the opportunity to contribute to proposals for market protections and other measures. They could provide expertise on particular diseases that might inform relevant discussions, according to a few participants. In the end social benefits are what matter, Steven Hyman said, and they differ from disease to disease. He provided the example of depression and the search for a treatment more efficacious than imipramine (a tricyclic antidepressant), which was first produced in 1957. Ideally, incentives would be created for the development of a drug with a novel mechanism of action that delivers more benefit to individuals with depression. For AD and PD, in contrast, incentives

would be generated for prevention trials. To maximize social benefit, different contexts need to be considered, said Hyman.

Advocacy agencies and nonprofit health organizations might even function as venture groups in certain settings, said Kiran Reddy. If a company does not have the internal resources to pursue every promising drug candidate, it might choose to partner with an advocacy group (or another company). Biogen is already exploring such arrangements in its work on AD. Along the same lines, Boutin mentioned that members of the National Health Council, an umbrella organization for patient advocacy groups, work with NIH-funded researchers who had products that showed great promise for treating particular conditions, but insufficient patent protection to bring to market.

Advocacy groups can potentially have significant impact by lobbying for what they consider appropriate measures. The Honorable Patrick Kennedy proposed that people rally around a "race to inner space" that would "unlock the mysteries of the mind and pave the way for therapies and cures for the most disabling of all illnesses, CNS illnesses." He strategized about how to assemble the equivalent of a NASA—an enterprise whose mission is to foster and support exploration of the brain rather than outer space—and emphasized the notion that such a venture must be a collective movement. It is time, Kennedy said, for groups that focus on individual nervous system disorders to join forces. "We have been so siloed by our diagnoses that we have failed to see that we have a more common cause," he said.

Kennedy charged workshop participants and their organizations with developing a proposal and then getting politicians to "go to [Capitol] Hill and the American people and make this case in the kind of way that hits not only our minds, but hits our hearts as well." He said that the issue is politically "bankable" because so many citizens are touched by brain disorders.

OPPORTUNITIES TO ENCOURAGE PATIENT INVOLVEMENT IN THE DRUG DEVELOPMENT PROCESS

- Encourage patient engagement with FDA to (1) address the risk/benefit trade-off between desired treatments and tolerable side effects, and (2) alleviate any other ethical concerns that arise (Boutin, Chiarello, Maderis, and others).

- Develop standardized definitions of value and allow patients to decide whether they want to pay more for a particular drug (Comas-Herrera, Longman).
- Work to creatively engage public–private partnerships that can advance and enhance "pull" incentives by providing patient input, building political will, and contributing other crucial resources (Boutin, Chiarello, Kennedy, and others).

A

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B

Workshop Agenda

Financial Incentives to Support Unmet Medical Needs for Nervous System Disorders: A Workshop

January 20–21, 2015

Institute of Medicine
Keck Center
500 Fifth Street, NW
Room 100
Washington, DC 20001

Background:

The global burden of nervous system disorders is projected to significantly increase over time and is estimated to cost society more than $6 trillion per year by 2030 (World Economic Forum and Harvard School of Public Health, 2011). Although there have been recent international initiatives to better understand the human brain in order to develop new therapeutics, several large pharmaceutical companies have decreased investment or even withdrawn from their neuroscience research programs. The perceived high risk and low probability of success has made the neuroscience sector less attractive than other therapeutics areas for research and development (R&D), despite the large market potential. As a result, patients are often left with few if any options for treatment and thus there is a need to consider policy options to increase private-sector investment in R&D for nervous system disorders. With this context this public workshop will explore opportunities to foster private-sector innovation by supporting

new investments directed toward the development of novel therapeutics to meet unmet needs for nervous system disorders.

Meeting Objectives:

The workshop will bring together key stakeholders to explore opportunities to increase private-sector investments directed toward the development of novel therapeutics to meet unmet needs for nervous system disorders. Presentations and discussions will be designed to:

- Examine opportunities and barriers to increasing investments for the development of novel therapeutics to support unmet medical needs for nervous system disorders.
  - Discuss specific considerations for combination therapies and disease-modifying treatments that may require extensive long-term prevention trials.
- Explore potential incentives that might lead to a significant reinvestment in R&D within the neuroscience sector, while considering the resources needed for implementation. For example,
  - Discuss regulatory changes that may help decrease the time it takes for a new central nervous system (CNS) drug to be approved.
  - Consider the impact of potential policy changes on patients.

SESSION I: OVERVIEW AND BACKGROUND

Session Objectives:

- Introduce the workshop objectives.
- Examine the current unmet medical needs for nervous system disorders.
- Provide a context for the current level of investment that CNS gets in comparison with other therapeutic areas.

January 20, 2015

8:30 a.m. **Welcome and Workshop Objectives**

DENNIS CHOI, *Workshop Co-Chair*
Professor and Chair, Department of Neurology, School of Medicine
Director, Neurosciences Institute
Stony Brook University

TIMOTHY COETZEE, *Workshop Co-Chair*
Chief Advocacy, Services, and Research Officer
National Multiple Sclerosis Society

8:45 a.m. **Overview of Unmet Medical Needs for Nervous System Disorders**

STEVEN HYMAN
Professor of Stem Cell and Regenerative Biology
Director, Stanley Center for Psychiatric Research
Broad Institute, MIT and Harvard University

9:15 a.m. **Policy-Based "Pull" Incentives for Creating Breakthrough CNS Drugs: Background *Neuron* Paper**

DENNIS CHOI, *Workshop Co-Chair*
Professor and Chair, Department of Neurology, School of Medicine
Director, Neurosciences Institute
Stony Brook University

9:45 a.m. **CNS Incentives in the Context of Other Therapeutic Areas**

DAVID MEEKER
President and Chief Executive Officer
Genzyme, A Sanofi Company

10:05 a.m. **Discussion with Speakers and Participants**
Moderators: Dennis Choi and Timothy Coetzee

10:30 a.m. BREAK

SESSION II: MARKET PROTECTIONS

Session Objectives:

- Consider the impact that increased intellectual property (IP) protections, including both enhanced data package protection and longer patent life, might have on private-sector investment in R&D for CNS disorders.
- Discuss the duration for enhanced IP protection that would be necessary to attract increased investment in the large-market CNS space.
- Examine the specific potential benefits and other impacts that enhanced IP protection could have on those with or at risk for CNS disorders.

10:45 a.m. **Overview of Current Intellectual Property Protections: Patents and Data Package Protection**

ROBERT ARMITAGE, *Session Chair*
IP Strategy and Policy Consultant
Former Senior Vice President & General Counsel, Eli Lilly and Company

11:05 a.m. **Panel Discussion: How Might New Market Protections Impact R&D Investment Decisions?**
Moderator: Robert Armitage

Discussion Questions:

- How do IP and technical issues interrelate to decide where both short- and long-term decision making affect allocation of resources?
- What are the current IP and market protections and why are they not working to incentivize CNS investments?
- What factors or policies might increase equity investments into this sector?

Panelists:

- Bonnie Weiss McLeod, Partner, Cooley, LLP
- Steven Paul, Chief Executive Officer and Board Member, Voyager Therapeutics; Weill Cornell Medical College
- Arti Rai, Professor of Law and Co-Director, Duke Law Center for Innovation Policy
- Kiran Reddy, Senior Director, Corporate Strategy, Biogen Idec

11:45 a.m. **Discussion with Panelists and Workshop Participants**

12:15 p.m. LUNCH

12:45 p.m. **Panel Discussion: Potential Policy Pathways and Their Implications**

Moderator: Ben Roin, Assistant Professor, MIT Sloan School of Management

Discussion Questions:

- What can be learned from other efforts to increase market exclusivity (e.g., Orphan Drug Act, MODDERN Cures Act, GAIN Act, and the Biosimilars Act)? Have they been successful?
- Is there a role for orphan drug-like registration exclusivity, priority review vouchers, or similar policies?
- What are the comparative benefits and potential drawbacks of enhancing patent protection versus greater data package protection as they relate to the CNS space?
- Should industry be expected to provide "give backs" in return for enhanced IP incentives and, if so, what might be appropriate (e.g., data sharing, publication of negative data)?

Panelists:

- Marc Boutin, Executive Vice President and Chief Operating Officer, National Health Council

- Alfred B. Engelberg, Trustee, The Engelberg Foundation
- William (Terry) Fisher, Wilmer Hale Professor of Intellectual Property Law, Faculty Director, Berkman Center for Internet and Society, Harvard Law School
- Nicholas Manetto, Director, FaegreBD Consulting

1:15 p.m. **Discussion with Panelists and Workshop Participants**

1:45 p.m. **Response Panel and Discussion with Participants**
Moderator: Robert Armitage

Discussion Question:

- What IP-related incentives would make a real and substantial difference in how biopharma enterprises evaluate potential investments in CNS?

Panelists:

- Marc Boutin, Executive Vice President and Chief Operating Officer, National Health Council
- Alfred B. Engelberg, Trustee, The Engelberg Foundation
- William (Terry) Fisher, Wilmer Hale Professor of Intellectual Property Law, Faculty Director, Berkman Center for Internet and Society, Harvard Law School
- Nicholas Manetto, Director, FaegreBD Consulting
- Bonnie Weiss McLeod, Partner, Cooley, LLP
- Steven Paul, Chief Executive Officer and Board Member, Voyager Therapeutics; Weill Cornell Medical College
- Arti Rai, Professor of Law and Co-Director, Duke Law Center for Innovation Policy
- Kiran Reddy, Senior Director, Corporate Strategy, Biogen Idec

2:45 p.m. BREAK

SESSION III: INCENTIVES THROUGH INNOVATIVE REGULATORY PATHWAYS

Session Objectives:

- Discuss opportunities to incentivize CNS R&D by using existing Food and Drug Administration authorities or through new regulatory mechanisms.
- Explore innovative applications of existing clinical development regulatory pathways and how they may be adopted for CNS drugs to decrease the length of clinical trials and the time it takes for a new drug to be approved.
- Consider the risks, benefits, and trade-offs of establishing accelerated and conditional approval pathways.

3:00 p.m. **Session Overview**

JANET WOODCOCK, *Session Chair*
Director, Center for Drug Evaluation and Research
Food and Drug Administration

3:10 p.m. **The Promise and Pitfalls of Changing Regulatory Standards to Spur CNS Drug Discovery**

AARON KESSELHEIM
Associate Professor of Medicine
Harvard Medical School and Brigham and Women's Hospital

3:25 p.m. **Six Opportunities for Improving Pathways to Market: A Global Perspective**

RAJ LONG
Senior Regulatory Officer-Integrated Development, Global Health
The Bill & Melinda Gates Foundation

3:40 p.m. **Panel Discussion: New or Existing Regulatory Approval Pathways**
Moderator: Janet Woodcock
Discussion Topics:

- Discuss whether and how existing regulatory pathways can be used by CNS drug developers.
- Discuss new or modified accelerated approval pathways to facilitate CNS drug development and how these innovations might alter risk and other ethical considerations.
- Explore innovations in clinical trials that could help reduce time, cost, and risk to expedite pathway to market.

Panelists:

- Jeff Allen, Executive Director, Friends of Cancer Research
- Lauren Chiarello, Senior Director, Federal Government Relations at National Multiple Sclerosis Society
- Jeffrey Jonas, Chief Executive Officer, SAGE Therapeutics
- Aaron Kesselheim, Harvard Medical School and Brigham and Women's Hospital
- Alex London, Professor of Philosophy and Director, The Center for Ethics and Policy, Carnegie Mellon University
- Raj Long, The Bill & Melinda Gates Foundation

4:20 p.m. **Discussion with Panelists and Workshop Participants**

5:00 p.m. **Adjourn Day 1**

January 21, 2015

SESSION IV: IMPACT OF FINANCIAL INNOVATION ON THE PATIENTS

Session Objectives:

- Identify issues that will need to be addressed in further depth related to how proposed incentives could potentially impact patient access to new treatments.
- Consider how innovation-friendly reimbursement and payment policies can ensure patient access to new medicines.
- Examine how the costs associated with increased financial incentives, including longer IP protection or data exclusivity, would impact patient access to innovative and generic medicines.
- Consider how access to new medicines may impact overall health care costs and other potential economic benefits.

8:30 a.m. **Session Overview**

GEORGE VRADENBURG, *Session Chair*
Chairman, Founding Board Member
USAgainstAlzheimer's

8:40 a.m. **Potential Impact of New Treatments on Health Care Costs**

Defining Value for Innovative Therapeutics to Meet Unmet Medical Needs for Nervous System Disorders

ROGER LONGMAN
Chief Executive Officer
Real Endpoints

Economic Cost and Impact of Nervous System Disorder Prevention and Treatment Strategies

ADELINA COMAS-HERRERA
Research Fellow
London School of Economics and Political Science

9:10 a.m. **Balancing Access, Value, and CNS Drug Risks:**

Societal Impact

Tension and Trade-Offs for Incentivizing Innovative Therapeutics

PETER UBEL
Professor of Business, Public Policy and Medicine
Duke University

Value and Costs of Innovative Therapies to Patients

GAIL MADERIS
President and Chief Executive Officer
BayBio

Practical Considerations with the Implementation of Innovative Medicines into Generally Accepted Practice That Is Reimbursable

RHONDA ROBINSON BEALE
Senior Vice President and Chief Medical Officer
Blue Cross of Idaho

9:55 a.m. **Discussion with Attendees**

10:30 a.m. BREAK

SESSION V: MEETING RECAP AND OPPORTUNITIES FOR IMPACTING CHANGES TO U.S. POLICY

Session Objectives:

- Recap the key themes presented and discussed during each session.
- Consider how the ideas discussed at the workshop can be implemented into U.S. policy.
- Discuss the role of each stakeholder (patients, academic societies, and the private sector) in helping to implement potential policy changes to incentivize CNS drug discovery and development.

Session Chairs: Dennis Choi and Timothy Coetzee

10:45 a.m. **Mobilizing a Path Forward: Translating Ideas into Policy**

HONORABLE PATRICK KENNEDY
Co-Founder, One Mind
The Kennedy Forum

11:00 a.m. **Discussion with Workshop Participants**

11:15 a.m. **Session Chairs II-IV: Presentation of Key Themes**

- Presentation by session chairs on key themes presented and discussed.
- What actions are needed to advance CNS drug discovery and development at a policy level?

ROBERT ARMITAGE
IP Strategy and Policy Consultant
Former Senior Vice President & General Counsel,
Eli Lilly and Company

JANET WOODCOCK
Director, Center for Drug Evaluation and Research
Food and Drug Administration

GEORGE VRADENBURG
Chairman, Founding Board Member
USAgainstAlzheimer's

11:55 a.m. **Discussion with Workshop Participants**

12:30 p.m. LUNCH

1:00 p.m. **Next Step Panels**

Discussion Questions:

- Who else needs to be brought into the conversation?
- What are practical steps individual groups can follow to advance the dialogue?

- What are sector-specific challenges and opportunities to advance policy?

1:00 p.m. **Next Steps: The Potential Role of Academic Societies to Advance Policy-Based Incentives for CNS Drug Discovery and Development**
Moderator: Walter Koroshetz, Acting Director, National Institute of Neurological Disorders and Stroke

Panelists:
- William Z. Potter, American College of Neuropsychopharmacology, National Institute of Mental Health
- Michael Rogawski, President, American Society for Experimental NeuroTherapeutics; University of California, Davis
- Edward F. Rover, Chairman and President, Dana Alliance for Brain Initiatives; Charles A. Dana Foundation
- Katie Sale, Executive Director, American Brain Coalition
- Paul Summergrad, President, American Psychiatric Association; Tufts University School of Medicine

2:00 p.m. **Next Steps: The Potential Role of Patient or Disease Advocacy Groups to Advance Policy-Based Incentives for CNS Drug Discovery and Development**
Moderator: Margaret Anderson, Executive Director, FasterCures

Panelists:
- Brian Fiske, Vice President, Research Programs, The Michael J. Fox Foundation for Parkinson's Research
- Stephen Johnson, Chief Policy Officer, One Mind
- Robert Ring, Chief Science Officer, Autism Speaks
- Andrew Sperling, Director of Federal Legislative Advocacy, National Alliance on Mental Illness

- William H. Thies, Senior Scientist in Residence, Medical and Scientific Relations, Alzheimer's Association
- George Vradenburg, Chair, Founding Board Member, USAgainstAlzheimer's

3:00 p.m. **Next Steps: The Potential Role of the Private Sector (Industry and Foundations) to Advance Policy-Based Incentives for CNS Drug Discovery and Development**
Moderator: Bernard H. Munos, Founder, InnoThink Center for Research in Biomedical Innovation; Faster-Cures

Panelists:

- Cartier Esham, Executive Vice President, Emerging Companies, Biotechnology Industry Organization
- Bruce Kinon, U.S. Therapeutic Head, Psychosis, Lundbeck LLC, USA
- Michele M. Oshman, Director, Federal Alliance Development, Corporate Affairs, Eli Lilly and Company
- Maike Stenull, Senior Director, Strategic Projects and Transformational Leadership, Office of the Chief Medical Officer, Johnson & Johnson
- David Wholley, Director, Research Partnerships, Foundation for the National Institutes of Health

4:00 p.m. **Discussion with Workshop Participants**

4:30 p.m. **Closing Remarks**

DENNIS CHOI, *Workshop Co-Chair*
Professor and Chair, Department of Neurology, School of Medicine
Director, Neurosciences Institute
Stony Brook University

TIMOTHY COETZEE, *Workshop Co-Chair*
Chief Advocacy, Services, and Research Officer
National Multiple Sclerosis Society

4:45 p.m. ADJOURN

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Registered Attendees

Lauriaselle Afanador
University of Maryland
School of Medicine

Neeraj Agarwal
National Eye Institute

Thompson Akwo
Health Consulting
International

Jeff Allen
Friends of Cancer Research

Margaret Anderson
FasterCures

Megan Anderson
CRD Associates

Robert Armitage
Eli Lilly and Company

Bruce Artim
Eli Lilly and Company

Carolyn Asbury
The Dana Foundation

Dan Barnes
FamilyWize Community
Service Partnership

Melissa Bartlett
Genzyme Corporation

Heather Bonsiero
Spectrum

Lizbet Boroughs
American Psychiatric
Association

Marc Boutin
National Health Council

Linda Brady
National Institute of Mental
Health

Neil Buckholtz
National Institute on Aging

Rosa Canet-Aviles
Foundation for the National Institutes of Health

Garry Carneal
The Kennedy Forum

C. Thomas Caskey
Baylor College of Medicine

Jingyan Chen
Genentech

Lauren Chiarello
National Multiple Sclerosis Society

Dennis Choi
Stony Brook University

Stacy Coen
Genzyme Corporation

Timothy Coetzee
National Multiple Sclerosis Society

Adelina Comas-Herrera
London School of Economics and Political Science

Jacqueline Corrigan-Curay
National Institutes of Health

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Center for Biomolecular Therapeutics

Safiyya Dharssi
Pfizer Inc.

Diane Dorman
National Organization for Rare Disorders

Cynthia Duggan
The New York Academy of Sciences

William Emmet
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Biotechnology Industry Organization

Brendan Fairfield
Next Chapter, LLC

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Harvard Law School

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The Michael J. Fox Foundation for Parkinson's Research

Stephen Fried
Columbia University Graduate School of Journalism

Sara Froelich
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Miriam Godwin
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Nirupa Goel
National Institutes of Health

Walter Greenleaf
Pear Therapeutics

Christina Hamilton
The lymphangioleiomyomatosis (LAM) Foundation

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MedStar National Rehabilitation Hospital

Ramona Hicks
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National Institute on Aging

Stuart Hoffman
Department of Veterans Affairs

Anna Husain
Threespot

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Broad Institute of Massachusetts Institute of Technology and Harvard University

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Janet Jenkins-Showalter
Genentech

Stephen Johnson
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Jeffrey Jonas
SAGE Therapeutics Inc.

Dorothy Jones-Davis
Foundation for the National Institutes of Health

Steven Kaminsky
International Rett Syndrome Foundation

Patrick Kennedy
One Mind and The Kennedy Forum

Aaron Kesselheim
Harvard Medical School and Brigham and Women's Hospital

Bruce Kinon
Lundbeck LLC, USA

Walter Koroshetz
National Institute of Neurological Disorders and Stroke

Kara Kukfa
The Kennedy Forum

Beth Lange
Personal Care Products Council

Gardiner Lapham
Citizens United for Research in Epilepsy

Patroski Lawson
Lundbeck LLC, USA

Jay Lombard
Genomind

Alex London
Carnegie Mellon University

Raj Long
The Bill & Melinda Gates Foundation

Roger Longman
Real Endpoints

Ashley Lusk
Threespot

Gail Maderis
BayBio

Nicholas Manetto
FaegreBD Consulting

Bruce Margetich
FamilyWize Community Service Partnership

Heddie Martynowicz
Janssen Research & Development, LLC

Bonnie Weiss McLeod
Cooley, LLP

David Meeker
Genzyme, a Sanofi Company

Les Meyer
Self-Employed

Robert Meyer
University of Virginia School of Medicine

Richard Mohs
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Meghan Mott
National Institute of Neurological Disorders and Stroke

Amy Muhlberg
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Bernard H. Munos
Innothink Center for Research in Biomedical Innovation; FasterCures

Anh Nguyen
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Mary O'Donovan
BioMarin Pharmaceutical Inc.

Michele M. Oshman
Eli Lilly and Company

Jennifer Palute
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Diana Pankevich
American Association for the Advancement of Science

Steven Paul
Weill Cornell Medical College; Voyager Therapeutics

Nicky Penttila
Dana Foundation

Matthew Peterson
PWR

William Z. Potter
American College of Neuropsychopharmacology; National Institute of Mental Health

Rana Quraishi
University of Maryland, Baltimore

Arti Rai
Duke University School of Law

Peter Reczek
National Institutes of Health

Kiran Reddy
Biogen Idec

Robert Ring
Autism Speaks

Diane Robertson
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Rhonda Robinson Beale
Blue Cross of Idaho

Michael Rogawski
University of California, Davis; American Society for Experimental Neurotherapeutics

Benjamin Roin
Massachusetts Institute of Technology; Sloan School of Management

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Charles A. Dana Foundation; Dana Alliance for Brain Initiatives

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Autism Speaks

Katie Sale
American Brain Coalition

Ameet Sarpatwari
Harvard Medical School and Brigham and Women's Hospital

Todd Sherer
The Michael J. Fox Foundation for Parkinson's Research

David Shurtleff
National Center for Complementary and Integrative Health

Phil Skolnick
National Institute on Drug Abuse

Maryann Smith
Participant

Andrew Sperling
National Alliance on Mental Health

Stuart Spielman
Autism Speaks

Maike Stenull
Johnson & Johnson

Laurie Stepanek
American University

Melissa Stevens
FasterCures

Evelyn Strauss
Freelance

V. S. Subrahmanian
University of Maryland

Paul Summergrad
Tufts University School of Medicine; American Psychiatric Association

Timothy Swope
FasterCures

William Thies
Alzheimer's Association

Ted Thompson
Parkinson's Action Network

Steve Tremitiere
FamilyWize Community Service Partnership

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Genentech

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Food and Drug Administration

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Strategic Regulatory Partners, LLC

Jerome Wujek
National Eye Institute

Sally Young
Lundbeck, LLC

Stevin Zorn
Lundbeck Research USA, Inc.

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Participant Biographies

Jeff Allen, Ph.D., serves as the executive director of Friends of Cancer Research (Friends), a think tank and advocacy organization in Washington, DC. Friends is one our country's leading voices in advocating for policies and developing solutions that will get treatments to patients in the safest and quickest way possible. As a thought leader on many issues related to the Food and Drug Administration, regulatory strategy, and health care policy, Dr. Allen is regularly published in prestigious medical journals and policy publications. In addition to participating in major scientific and policy symposiums around the country each year, Dr. Allen testifies before Congress and contributes his expertise to the legislative process on multiple occasions. Recent Friends initiatives include the establishment of the new Breakthrough Therapies designation and the development of the Lung Cancer Master Protocol, a unique partnership that will accelerate and optimize clinical trial conduct for new drugs. He also serves on a variety of influential committees, boards, and advisory councils. Dr. Allen received his Ph.D. in Cell and Molecular Biology from Georgetown University and his B.S. in Biology from Bowling Green State University.

Margaret Anderson, M.S., serves as executive director of FasterCures, a Milken Institute center that works to speed up the process of getting new medicines from discovery to patients. She is a founding board member and past president of the Alliance for a Stronger FDA [Food and Drug Administration]; a member of the National Institutes of Health National Center for Advancing Translational Sciences Advisory Council and Cures Acceleration Network Review Board, the National Health Council Board of Directors, United for Medical Research Steering Committee,

and the Institute of Medicine's Forum on Drug Discovery, Development, and Translation. Previously, Ms. Anderson was the deputy director and team leader of the Center on AIDS & Community Health at the Academy for Educational Development; program director at the Society for Women's Health Research; health science analyst at the American Public Health Association; and analyst and project director at the Congressional Office of Technology Assessment in the Biological Applications Program. Ms. Anderson holds a bachelor's degree from the University of Maryland and a master's Degree in Science, Technology, and Public Policy from George Washington University.

Robert Armitage, J.D., M.S., is a consultant on intellectual property (IP) policy and strategy. He completed a decade of service as senior vice president and general counsel for Eli Lilly and Company at the end of 2012. Prior to assuming his general counsel role at Lilly, Mr. Armitage had been Lilly's vice president and general patent counsel. Before his Lilly career, he spent 6 years as a partner in the Washington, DC, office of Vinson & Elkins LLP (1993–1999), where he established and led its DC-based IP practice. Among other positions, he has served as an adjunct professor of law at George Washington University Law School (1996–2000), a member of the Board of Directors of Human Genome Sciences, Inc. (1995–1999), president of the Board of Directors of Hospice Care of Southwest Michigan, Inc. (1985–1987), and chief intellectual property counsel for The Upjohn Company (1983–1993), where he began his professional career as a patent trainee in 1974. He has served in a variety of leadership positions in the intellectual property bar, including as president of both the American Intellectual Property Law Association (AIPLA) and the Association of Corporate Patent Counsel. Other leadership positions include service as chair of the following organizations: the American Bar Association Intellectual Property Law Section, the National Council of Intellectual Property Law Associations, the Fellows of the American Intellectual Property Law Association, the Patent Committee of the Pharmaceutical Research and Manufacturers of America (PhRMA), the Intellectual Property Committee of the National Association of Manufacturers, and the Intellectual Property Law Section of the State Bar of Michigan. He has also served as a member of the board of directors of both Intellectual Property Owners and the National Inventors Hall of Fame Foundation. Mr. Armitage currently serves as a member of the Advisory Board for the *Bloomberg BNA Patent Trademark & Copyright Journal*. He served as a trustee for Albion College,

which awarded him its Distinguished Alumni Award in 2006, and as a member of the Advisory Committee on International Economic Policy to the U.S. Department of State. He has received numerous recognitions for his work in the IP field. In 2004, the American Intellectual Property Law Association awarded him its highest recognition for lifetime achievement in intellectual property, the AIPLA Excellence Award. In 2008, the New Jersey Intellectual Property Law Association awarded Armitage its Jefferson Medal, an award recognizing exceptional contributions to the field of intellectual property. More recently, Mr. Armitage was inducted into the IP Hall of Fame in recognition of his decades-long advocacy of legislation to modernize the U.S. patent system and, in 2013, *Managing Intellectual Property Magazine* presented Armitage with its Outstanding Achievement in IP Award, recognizing the role he played in the successful effort to enact the America Invents Act, which made the most sweeping changes to U.S. patent law in the past 175 years.

Marc Boutin, J.D., is the executive vice president and chief operating officer of the National Health Council, an organization that brings together all segments of the health care community to provide a united voice for the more than 133 million people with chronic diseases and disabilities and their family caregivers. In addition to overseeing financial management and operations at the National Health Council, Mr. Boutin builds consensus among member patient advocacy organizations, enabling them to speak with one voice on systemic health research and health care policy initiatives. This results in legislation and regulations that address the collective needs of patients and their family caregivers. In addition, he provides guidance to patient organizations on various association issues, including corporate structure, government relations, fundraising, and outreach. He has been actively involved in health advocacy, policy, and federal and state legislation throughout his career. He is a member of the International Alliance of Patients' Organizations Governing Board, Community Health Charities Board of Directors, Patient-Centered Outcomes Research Institute (PCORI) Advisory Panel on Patient Engagement, Sanofi Partners in Patient Health Global Council, and the North America Advisory Board to the Drug Information Association.

Lauren Chiarello, M.P.H., serves as Senior Director for Federal Government Relations at the National Multiple Sclerosis Society (NMSS), where she drives and advances policy initiatives that could impact the full spectrum of multiple sclerosis (MS) research and access to approved

therapies. She is responsible for identifying, tracking, and engaging in relevant legislative and/or regulatory opportunities that could either create incentives for, or create barriers to, MS research. In past years, she has served in a variety of leadership positions in national coalitions, including leading the National Health Council's Food and Drug Administration (FDA) Affinity Group and serving as a member of the Independence Through Enhancement of Medicare and Medicaid Coalition (ITEM) steering committee. Currently, she chairs the National Health Council's Government Relations Affinity Group. Prior to joining the NMSS Society, she was a senior associate of health policy at Avalere Health, where she conducted quantitative and qualitative research on health system trends. In this role, she primarily analyzed Medicare, FDA, and health care reform policies for a wide array of nonprofit and commercial clients. She also worked at the National Association of County & City Health Officials, where she helped to coordinate its national conference. She has a master's degree in Public Health from George Washington University and a bachelor's degree in Public Policy from Vanderbilt University.

Dennis Choi, M.D., Ph.D., is professor and chair of the Department of Neurology and director of the Neurosciences Institute at Stony Brook University, as well as director of the Brain Sciences Institute at the Korea Institute of Science and Technology. Prior positions have included executive vice president at the Simons Foundation, vice president for Academic Health Affairs at Emory University, executive vice president for Neuroscience at Merck Research Labs, and head of neurology at Washington University Medical School. A Fellow of the American Association for the Advancement of Science (AAAS) and member of the Institute of Medicine, he has served previously as president of the Society for Neuroscience, vice president of the American Neurological Association, and chair of the U.S./Canada Regional Committee of the International Brain Research Organization. He has been a member of the National Academy of Sciences Board on Life Sciences, and the Councils for the National Institute of Neurological Disorders and Stroke, the National Institute on Aging, the Society for Neuroscience, the Winter Conference for Brain Research, the International Society for Cerebral Blood Flow and Metabolism, and the Neurotrauma Society. Past or present advisory board service includes the Dana Alliance for Brain Research, the Cure Alzheimer's Fund, the Christopher Reeve Paralysis Foundation, the Grass Foundation, the Hereditary Disease Foundation, the Harvard–

Massachusetts Institute of Technology (MIT) Program in Health Sciences and Technology, the Max-Planck Institute in Heidelberg, the Korea Institute for Advanced Study, and the Food and Drug Administration, as well as multiple university-based research consortia, biotechnology companies, and pharmaceutical companies. He received his M.D. from the Harvard–MIT Health Sciences and Technology Program, as well as a Ph.D. in Pharmacology and Neurology Training from Harvard.

Timothy Coetzee, Ph.D., is chief advocacy, services, and research officer of the National Multiple Sclerosis Society (NMSS), which he joined in 2000. In this capacity he leads mission delivery in the areas of state and federal advocacy, service, and care management programs for people with multiple sclerosis (MS), as well as the Society's research program, which funds more than 375 academic and commercial research projects around the world. Most recently, he served as president of Fast Forward, a venture philanthropy of NMSS, where he was responsible for the Society's strategic funding of biotechnology and pharmaceutical companies as well as partnerships with the financial and business communities. Prior to Fast Forward, Dr. Coetzee led the Society's translational research initiatives on nervous system repair and protection in multiple sclerosis. He is a member of the Institute of Medicine's Forum on Neuroscience and Nervous System Disorders and serves on the Board of Directors of the American Society of Experimental Neurotherapeutics. He also chairs the Integration Panel for the MS Research Program of the Department of Defense Congressionally Directed Medical Research Program. Dr. Coetzee received his Ph.D. in Molecular Biology from Albany Medical College in 1993 and has since been involved in the field of multiple sclerosis research.

Adelina Comas-Herrera is a current Research Fellow at the London School of Economics and Political Science and also serves as the academic project manager of the Modelling Dementia (MODEM) research project, which aims to estimate the impact, in terms of costs and quality of life, of making interventions that are known to work for people with dementia and their caregivers more widely available. Her current work focuses on the economics of dementia care, particularly the impact on unpaid caregivers. She has previously worked on making projections of future long-term care for the United Kingdom and other countries, and also on evaluating the potential role of private insurance and private/public partnerships in long-term care financing. Between 2010 and 2013, she was chair of the Westgate Community Trust (Canterbury), a

voluntary position. She is a Fellow of the Royal Society of Arts, Manufacturing and Commerce.

Alfred B. Engelberg, J.D., is an intellectual property lawyer. During a legal career of more than 40 years, he was a Patent Examiner in the U.S. Patent Office; a patent agent at Exxon Research & Engineering Co.; a patent trial attorney in the U.S. Department of Justice; and a member of the New York City law firm of Amster, Rothstein & Engelberg. He served as outside counsel to the Generic Pharmaceutical Association and played a leading role in the negotiations that passed the Hatch-Waxman Act of 1984, the landmark legislation that created the modern generic drug industry. Subsequently, he specialized in pharmaceutical patent litigation. In 1991, Engelberg founded the Engelberg Foundation to provide grants for innovative health care, youth development, and social service projects. It provided the concept and funding for the creation of *Consumer Reports* Best Buy Drugs; the Engelberg Center for Healthcare Reform at the Brookings Institution; and the Engelberg Center on Innovation Law and Policy at New York University (NYU) School of Law. Engelberg serves as a Trustee of NYU School of Law and the Brookings Institution and has served on many other nonprofit boards. He has retired from the practice of law, but remains active as a writer, adviser, and speaker on policy issues related to affordable medicines and intellectual property rights in the United States and around the world.

Cartier Esham, Ph.D., serves as executive vice president for emerging companies at the Biotechnology Industry Organization (BIO). In this role, Dr. Esham manages and directs BIO's policy development, advocacy, research, and educational initiatives for BIO's emerging companies, approximately 90 percent of BIO's membership. This includes capital formation policy and health policy impacting emerging companies, as well as research and analysis of the biopharmaceutical industry and life-science investment and financing. She has published papers in peer-reviewed science journals on water quality, marine microbial ecology, and bacterial phylogeny. Dr. Esham has a Ph.D. in Microbiology from the University of Georgia, a master's degree in Marine Biology from the University of North Carolina at Wilmington, and a B.S. from the University of Kentucky.

William Fisher, Ph.D., J.D., is the Wilmer Hale Professor of Intellectual Property Law and director of the Berkman Center for Internet and So-

ciety at Harvard University. Previously, he served as a law clerk to Judge Harry T. Edwards of the U.S. Court of Appeals for the D.C. Circuit and then to Justice Thurgood Marshall of the U.S. Supreme Court. His academic honors include a Danforth Postbaccalaureate Fellowship and a Post-Doctoral Fellowship at the Center for Advanced Study in the Behavioral Sciences in Stanford, California. Dr. Fisher received his undergraduate degree in American Studies from Amherst College and his graduate degrees (J.D. and Ph.D. in the History of American Civilization) from Harvard University.

Brian Fiske, Ph.D., currently serves as vice president, research programs, for The Michael J. Fox Foundation for Parkinson's Research, where he co-manages a team of research professionals who stay closely linked to the research community in order to develop an aggressive and innovative agenda for accelerating research and drug development for Parkinson's disease. This ensures that research priorities reflect and best serve the ultimate needs of patients. Dr. Fiske regularly meets with academic and industry researchers around the world to identify promising proposals to support, providing troubleshooting and ongoing management of projects as they go forward. After completing postdoctoral research at Columbia University, he spent several years as an editor for the scientific journal, *Nature Neuroscience*. Dr. Fiske earned an undergraduate degree in Biology from Texas A&M University and a Ph.D. in Neuroscience from the University of Virginia.

Steven Hyman, M.D., M.A., is director of the Stanley Center for Psychiatric Research at the Broad Institute of Massachusetts Institute of Technology and Harvard University, a core faculty member of the Broad Institute, and Harvard University Distinguished Service Professor of Stem Cell and Regenerative Biology. From 2001 to 2011, he served as provost of Harvard University. As provost he had a special focus on development of collaborative initiatives in the sciences and engineering spanning multiple disciplines and institutions. From 1996 to 2001, he served as director of the National Institute of Mental Health, where he emphasized investment in neuroscience and emerging genetic technologies. He also initiated a series of large practical clinical trials, including an emphasis on children, a population about which little was known. Dr. Hyman is the editor of the *Annual Review of Neuroscience*, founding president of the International Neuroethics Society (2008-2014), president (2015) of the Society for Neuroscience, and a member of the Institute of

Medicine, of the U.S. National Academies where he serves on the Council, is a member of the Board of Health Science Policy, and chairs the Forum on Neuroscience and Nervous System Disorders. He is a Fellow of the American Academy of Arts and Sciences; a Fellow of the American Association for the Advancement of Science; a Fellow of the American College of Neuropsychopharmacology; and a Distinguished Life Fellow of the American Psychiatric Association. Dr. Hyman received his B.A. summa cum laude from Yale College; a B.A. and an M.A. from the University of Cambridge, which he attended as a Mellon Fellow; and an M.D. cum laude from Harvard Medical School.

Stephen Johnson, J.D., M.A., is the chief intellectual property (IP) and policy officer for One Mind. Mr. Johnson works on strategies that drive One Mind's goals of hastening cures for patients through encouraging and enabling data sharing within and across disciplines; addressing barriers to data sharing on policy and technology levels; creating efficient public/private partnerships to leverage public, private, and philanthropic resources to advance research and cures; and focusing on incentives to innovation in neuroscience. Before joining One Mind, Mr. Johnson had more than 30 years of experience in IP law at Kirkland & Ellis LLP, where he was a founding partner of its New York and San Francisco offices and the former head of its New York and San Francisco IP. He began his career at Bird & Bird in London. Mr. Johnson obtained a degree in Natural Sciences (Genetics) from Cambridge University in England, and graduated from law schools in London and Chicago.

Jeff Jonas, M.D., joined SAGE as CEO in 2013 and has more than 20 years of experience on both the scientific and business sides of the pharmaceutical and health care industries, particularly in the central nervous system field. Before joining the SAGE team, he served as president of the Regenerative Medicine Division of Shire Plc and previously as senior vice president of research and development, Pharmaceuticals at Shire. Earlier, he served as executive vice president of ISIS Pharmaceuticals; as chief medical officer and executive vice president of Forest Laboratories, Inc.; and in senior-level positions at Upjohn Laboratories. Dr. Jonas founded AVAX Technologies, where he served as CEO and president, and SCEPTOR Industries, where he served as chair, president, and chief technology officer. Previously, he was independent director at Cara Therapeutics, Inc., and director of AVAX Technologies. He has published more than 70 scientific papers and chapters; authored more than

100 books, scientific articles, and abstracts; and received numerous awards. He received his B.A. from Amherst College and his M.D. from Harvard Medical School. He completed a residency in Psychiatry at Harvard and then served as Chief Resident in Psychopharmacology at McLean Hospital, Harvard Medical School.

The Honorable Patrick Kennedy served in the U.S. House of Representatives (D-RI) for 16 years and is predominantly known as author and lead sponsor of the Mental Health Parity and Addiction Equity Act of 2008. This legislation provides tens of millions of Americans who were previously denied care with access to mental health treatment. Now, Rep. Kennedy is the co-founder of One Mind, a national coalition seeking new treatments and cures for neurologic and psychiatric diseases of the brain afflicting one in every three Americans. One Mind is dedicated to enhancements in funding and collaboration in research across all brain disorders in the next decade. This endeavor unites efforts of scientists, research universities, government agencies, and industry and advocacy organizations throughout the world. Rep. Kennedy is bringing everyone together to design the first blueprint of basic neuroscience, and to guide efforts in seeking cures for neurological disorders affecting Americans. Rep. Kennedy is the founder of the Kennedy Forum on Community Mental Health, which served as a vehicle to celebrate the 50th anniversary of President Kennedy's signing of the Community Mental Health Act, the landmark bill that laid the foundation of contemporary mental health policy and provided Patrick Kennedy with the platform to launch a bold, ongoing effort to advance the work President Kennedy began. The Kennedy Forum continues to advocate for mental health parity.

Aaron Kesselheim, M.D., J.D., M.P.H., is an associate professor of medicine at Harvard Medical School and a faculty member in the Division of Pharmacoepidemiology and Pharmacoeconomics in the Department of Medicine at Brigham and Women's Hospital (BWH). His research focuses on the effects of intellectual property laws and regulatory policies on pharmaceutical development, the drug approval process, and the costs, availability, and use of prescription drugs both domestically and in resource-poor settings. At BWH, Dr. Kesselheim leads the Program On Regulation, Therapeutics, And Law (PORTAL), an interdisciplinary research core focusing on intersections among prescription drugs and medical devices, patient health outcomes, and regulatory practices and the law. In 2013, Dr. Kesselheim was named a Greenwall Fac-

ulty Scholar in Bioethics by the Greenwall Foundation, which supports innovative empirical research in bioethics. His work was also recently funded by the Harvard Program in Therapeutic Science, the Food and Drug Administration, and by a Robert Wood Johnson Foundation Investigator Award in Health Policy Research. He has testified numerous times before Congress on pharmaceutical policy and medical device regulation, and has consulted for the National Institutes of Health, Institute of Medicine, U.S. Patent and Trademark Office, and various state government offices. In 2012, he was named to the Perspectives Advisory Board of the *New England Journal of Medicine*. Dr. Kesselheim also is a faculty supervisor for the Petrie-Flom Center for Health Law Policy, Biotechnology, and Bioethics at Harvard Law School, the Harvard Center for Bioethics, and is a research associate in the Department of Health Policy and Management at the Harvard School of Public Health. For the 2014–2015 academic year, he was appointed as a Visiting Associate Professor of Law at Yale Law School, where he taught Food and Drug Administration Law. He is Board Certified in Internal Medicine, working as a primary care physician at the Phyllis Jen Center for Primary Care at BWH.

Bruce Kinon, M.D., is the U.S. Therapeutic Head, Psychosis, at Lundbeck LLC, the U.S. affiliate of the global pharmaceutical company H. Lundbeck A/S headquartered in Denmark. Lundbeck is engaged in the research and development, production, marketing, and sale of drugs for the treatment of disorders in the central nervous system and is committed to improve the quality of life of people suffering from psychiatric and neurological disorders. Dr. Kinon's responsibilities include the development of innovative drug treatments for schizophrenia and the effective delivery into clinical practice of new pharmacologic therapies for psychoses. He has had a long and productive career in the field of neuropsychopharmacology spanning many years in academic research and practice at the Long Island Jewish–Hillside Medical Center in New York, a National Institute of Mental Health center of schizophrenia research, and in pharmaceutical drug development, first at Eli Lilly and Company, where he led in part the development and commercialization of the eminently successful, atypical antipsychotic drug Zyprexa and later the development of novel glutamate-based schizophrenia therapies, and now at Lundbeck LLC. Dr. Kinon is an internationally recognized expert who has contributed significantly to safety and efficacy assessments, outcomes research, global marketing, and comprehensive knowledge of the schizophrenia disease state. He has published exten-

sively in internationally recognized peer-reviewed journals and is an often-invited chair or participant in panels at international psychopharmacology scientific congresses. Dr. Kinon received his M.D. training at the New York University (NYU) School of Medicine and completed his residency in Psychiatry at the NYU-Bellevue Hospital Medical Center.

Walter Koroshetz, M.D., became acting director of National Institute of Neurological Disorders and Stroke (NINDS) in 2014. Previously, he served as deputy director under Dr. Story Landis. Together, they directed program planning and budgeting, and oversaw the scientific and administrative functions of the Institute. He has held leadership roles in a number of the National Institutes of Health (NIH) and NINDS programs, including NIH's BRAIN Initiative, the Traumatic Brain Injury Center collaborative effort between the NIH intramural program and the Uniformed Services University of the Health Sciences, and the multiyear effort to develop and establish the NIH Office of Emergency Care Research to coordinate research and research training. Before joining NINDS, Dr. Koroshetz served as vice chair of the neurology service and director of stroke and neurointensive care services at Massachusetts General Hospital (MGH). He was a professor of neurology at Harvard Medical School (HMS) and led neurology resident training at MGH between 1990 and 2007. During that time he co-directed the HMS Neurobiology of Disease Course with Drs. Edward Kravitz and Robert H. Brown. Dr. Koroshetz graduated from Georgetown University and received his M.D. from the University of Chicago. He trained in internal medicine at the University of Chicago and MGH. He trained in neurology at MGH, after which he did post-doctoral studies in cellular neurophysiology at MGH with Dr. David Corey, and later at the Harvard neurobiology department with Dr. Edward Furshpan, studying mechanisms of excitoxicity and neuroprotection. He joined the neurology staff, first in the Huntington's disease (HD) unit, followed by the stroke and neurointensive care service. A major focus of his clinical research career was to develop measures in patients that reflect the underlying biology of their conditions. With the MGH team he discovered increased brain lactate in HD patients using MR spectroscopy. He helped the team pioneer the use of diffusion/perfusion-weighted MR imaging and CT angiography/perfusion imaging in acute stroke. Active in the American Academy of Neurology (AAN), Dr. Koroshetz chaired its public information committee, led its efforts to establish acute stroke therapy in the United States, founded the Stroke Systems Working Group, and was a member of the AAN Board of Directors.

Alex John London, Ph.D., is professor of philosophy and director of The Center for Ethics and Policy at Carnegie Mellon University. Professor London is an elected Fellow of the Hastings Center, whose research focuses on foundational ethical issues in human-subjects research, on issues of social justice in the transnational context, and on methodological issues in theoretical and applied ethics. He is the author of more than 50 papers, which have appeared in *Mind*, *Science*, *Lancet*, *PLoS Medicine*, and numerous other journals and collections. He is co-editor of *Ethical Issues in Modern Medicine*, one of the most widely used textbooks in medical ethics. In 2012, Professor London joined the Working Group on the Revision of the Council for International Organizations of Medical Sciences 2002 International Ethical Guidelines for Biomedical Research Involving Human Subjects. In 2011, he was appointed to the Steering Committee on Forensic Science Programs for the International Commission on Missing Persons. Since 2007 he has served as a member of the Ethics Working Group of the HIV Prevention Trials Network. He has testified before the Presidential Commission for the Study of Bioethical Issues and has been commissioned to write papers for the Centers for Disease Control and Prevention and the Institute of Medicine. He has served as an ethics expert in consultations with numerous national and international organizations, including the National Institutes of Health, the World Health Organization, the World Medical Association, and the World Bank.

Raj Long, M.S., M.Sc., is a senior executive with more than 20 years of experience in the pharmaceutical industry. She offers a wide range of expertise in regulatory strategy, and has worked with the Food and Drug Administration, European Medicines Agency, Council of Federal Domestic Assistance, and other Brazil, the Russian Federation, India and China regulatory authorities. She is currently a senior regulatory officer at The Bill & Melinda Gates Foundation, where she works in malaria and neglected infectious diseases. Previously, she was the global head of regulatory GE Healthcare-MDx in the United Kingdom, responsible for regulatory organization and access in Europe, Middle East, Africa, the Americas, and Asia. Prior to joining GE Healthcare, Ms. Long was vice president of Regulatory International AGL both in Novartis, Switzerland, and at Bristol-Myers Squibb, Princeton, New Jersey. She was responsible for implementing strategic organizational models in Asia, Latin America, Middle East, and Africa with a strategic focus on early access. In 2014, she was invited by the U.K. Secretary of State to be a member to the

World Dementia Council as a global regulatory expert. In addition, she was appointed by the U.K. government as director, integrated development to lead innovative approaches in the regulatory development of clinically relevant therapies for dementia. She has a double master's in Psychology and in Nursing Education from the University of Glasgow and Edinburgh, Scotland, respectively.

Roger Longman, M.A., is CEO of Real Endpoints, a start-up company focused on pharmaceutical reimbursement, and aiming to help both payers and product developers improve the value of pharmacotherapy. Its first product assesses—systematically, objectively, and transparently—the value of drugs relative to their competitors. Until 2009, Mr. Longman was managing director, pharma at Elsevier Business Intelligence, a Reed Elsevier company. He has been involved with the health care industry for more than 25 years. From 1990 through 2008, Mr. Longman was co-CEO and managing director of Windhover, an information company providing sophisticated analysis and data on pharmaceutical and medical device business strategy through publications, databases, and conferences. Mr. Longman co-founded and built the company through internal development (with publications, e.g., *IN VIVO*, *Start-Up*, and *The RPM Report*; several databases, including The Strategic Transactions Database; and a series of senior-executive conferences), and through acquisition. In 2008, Windhover was acquired by Reed Elsevier and merged with its FDC Reports division (publishers of *The Pink Sheet*, *The Gray Sheet*, and many other medical industry newsletters), creating Elsevier Business Intelligence. Mr. Longman ran the combined group's pharmaceutical business until he left in 2010 to begin working on Real Endpoints with Norman Selby, who had been Windhover's chair and lead investor.

Gail Maderis, M.B.A., is president and CEO of BayBio, the industry organization representing and supporting Northern California's life science community. As a former biotech CEO, she brings deep experience and commitment to supporting the industry through enterprise development, peer-to-peer experience sharing, and advocacy and support of education and workforce development. From 2003 to 2009, Ms. Maderis served as president and CEO of Five Prime Therapeutics, Inc., a privately held protein discovery and development company. At Five Prime, she successfully funded the company's rapid growth through substantial private equity financings and corporate partnerships and took the compa-

ny's first novel cancer therapeutic from discovery into clinical trials. Prior to Five Prime, she held senior executive positions at Genzyme Corporation, including founder and president of Genzyme Molecular Oncology. She practiced management and strategy consulting with Bain & Co. Ms. Maderis serves on the boards of NovaBay Pharmaceuticals, Opexa Therapeutics, BayBio, the Mayor's Biotech Advisory Council of San Francisco, and the HBS Healthcare Initiative. She earned a B.S. in Business from University of California, Berkeley, and an M.B.A. from Harvard Business School.

Nicholas Manetto designs, directs, and implements successful public policy advocacy campaigns. With more than a decade in government affairs, public policy, and strategic communications, he is an experienced strategist in the process of high-stakes initiatives from start to finish. Mr. Manetto manages client teams and projects focused on health care delivery and payment models, biomedical research, drug development, and public health. His work spans projects focused on Congress as well as federal departments and agencies. Frequently, initiatives include a public or media component through crafting and placing op-eds, designing and launching campaign websites, and a variety of traditional and new media strategies and tactics. Many of these projects are coalitions designed to bring multiple diverse voices to an issue.

Bonnie Weiss McLeod, Ph.D., J.D., is a Partner in the Intellectual Property Practice Group for Cooley, LLP, bringing her in-depth experience serving the life science industry in the prosecution of biotechnology and pharmaceutical patent applications. She has managed many intellectual property due diligence analyses in collaboration with other Cooley partners in relation to public offerings, venture capital financing, and life science corporate transactions. Dr. McLeod specializes in counseling clients ranging from non-profits and small to mid-size biotech companies with regard to developing and maintaining a patent strategy that is consistent with business goals. Dr. McLeod is a former patent examiner in the biotechnology group of the U.S. Patent and Trademark Office. Her practice focuses on the biotechnology arts, including molecular biology, cellular biology, bacterial and eukaryotic genetics, immunology and autoimmunity, neuroscience, recombinant antigens and vaccines, gene therapy, genetic engineering, genomics, microarray technologies, virology, and RNA interference. Dr. McLeod is a graduate of the Columbus School of Law at Catholic University of America (CUA), where she

graduated magna cum laude. She is currently an adjunct professor at CUA, where she teaches a course on patent prosecution. Dr. McLeod is admitted to practice in Virginia, Washington, DC, and before the U.S. Patent and Trademark Office, and is a member of American Intellectual Property Law Association and the American Bar Association. She serves on the pro bono committee for Cooley's Washington, DC, office and is actively involved in various pro bono matters. She is a frequent speaker at universities and local life science organizations and has spoken on topics such as developing a global patent strategy, the business side of intellectual property, joint inventorship issues, developing a patent portfolio that will attract investors, and the Myriad and Prometheus Supreme Court decisions. Dr. McLeod was awarded her Ph.D. in Molecular Biology from the University of Maryland College Park. Dr. McLeod also completed post-doctoral work in the study of molecular mechanisms of co-stimulatory signaling in T-cells.

David Meeker, M.D., was appointed president and chief executive officer of Genzyme in 2011. Genzyme is a global biotechnology company committed to discovering and delivering transformative therapies for patients with rare and special unmet medical needs. Dr. Meeker oversees and provides the vision for the company's two business units—Rare Diseases and Multiple Sclerosis—as well as its long-standing relationships with patient communities and dedicated workforce of nearly 10,000 employees. In his career with Genzyme, Dr. Meeker has held key positions of increasing responsibility, most recently as chief operating officer. In this role, he was responsible for Genzyme's commercial organization, overseeing its business units¸ country management organization, and global market access functions. As chief operating officer, he played an important role in the integration with Sanofi. Dr. Meeker joined Genzyme in 1994 as medical director to work on the Cystic Fibrosis Gene Therapy program. Subsequently, as Vice President, medical affairs, he was responsible for the development of rare disease therapies that today represent transformative and life-saving advancements in medicine for patients. Prior to joining Genzyme, Dr. Meeker was the director of the Pulmonary Critical Care Fellowship at the Cleveland Clinic and an assistant professor of medicine at Ohio State University. He has authored more than 40 articles and multiple book chapters. Dr. Meeker received his M.D. from the University of Vermont Medical School. He completed the Advanced Management Program at Harvard Business School in 2000.

Bernard H. Munos, M.B.A., M.S., is a Senior Fellow at FasterCures, a center of the Milken Institute, and the founder of the InnoThink Center for Research in Biomedical Innovation, a consultancy that helps biomedical research organizations become better innovators. Before that, he served as an advisor for corporate strategy at Eli Lilly, where he focused on disruptive innovation and the radical redesign of research and development. He is also a member of National Center for Advancing Translational Sciences' Advisory Council and Cures Acceleration Network, a non-executive director of Glenmark Pharmaceuticals, a member of the Advisory Board of Science Translational Medicine, and an advisor to or board member of a dozen other companies or publicly financed research organizations. His research has been profiled by *Forbes* magazine; he blogs about biomedical innovation on the *Forbes* and FasterCures websites; and the popular industry newsletter *FiercePharma* named him 1 of the 25 most influential people in biopharma. He received his M.B.A. from Stanford University and holds other graduate degrees in Animal Science and Agricultural Economics from the Paris Institute of Technology for Life, Food and Environmental Sciences and the University of California, Davis.

Michele M. Oshman, Pharm.D., director of federal advocacy relations for Eli Lilly and Company, works in the company's Washington, DC, office. Dr. Oshman joined Lilly in 2002 as a clinical neuroscience researcher and has served in multiple clinical development and corporate leadership roles. She earned a Six Sigma Black Belt in 2005 and led multiple transformational efforts across the company. She joined the Advocacy team in 2007 and now leads Lilly's policy engagement with a large portfolio of patient advocacy groups, professional societies, and trade associations. She serves as a strategic advisor to multiple business unit leaders and senior leadership, and in 2012, she was appointed chair of the BIO Alliance Development section. Prior to joining Lilly, Dr. Oshman conducted clinical research under former National Institute on Drug Abuse Director Dr. Robert Dupont. Dr. Oshman serves on the Boards of Directors for the National Alliance on Caregiving, the American Brain Coalition, and Green Door. She also chairs the Arthritis Foundation and Arthritis Industry Forum and sits on multiple corporate advisory councils for national and international advocacy organizations. In 2013, she was appointed to the Board of Directors of Green Door, a Washington, DC, community mental health center. She works with honorary Green Door leadership, including former members of Congress and other prominent

community members on strategic initiatives to ensure that area residents struggling with severe persistent mental illnesses can access timely and high-quality treatment, regardless of their financial situation. A 1993 graduate of American University in Washington, DC, where she studied Political Science and Communication, Dr. Oshman pursued a Doctor of Pharmacy at the University of Maryland, Baltimore.

Steven Paul, M.D., M.S., is Voyager Therapeutics' president and CEO, a member of the Board of Directors, and a venture partner at Third Rock Ventures. Dr. Paul brings to Voyager more than 35 years of neuroscience expertise and an extensive track record in central nervous system drug discovery and development. As a venture partner at Third Rock, he helps lead the ideation and development of new companies, including Voyager. Before joining Voyager as CEO, Dr. Paul was the founding director of the Appel Alzheimer's Disease Research Institute, where he was the Principal Investigator of the Institute's novel adeno-associated virus gene therapy program for Alzheimer's disease, as well as professor of neuroscience, psychiatry, and pharmacology at Weill Cornell Medical College. Earlier, he spent 17 years at Eli Lilly, during which time he held several key leadership roles, including president of the Lilly Research Laboratories and vice president of discovery research and neuroscience research. As president of the Lilly Research Laboratories, he was responsible for the company's overall research and development strategy, expanding its efforts in oncology and biotechnology and resulting in a pipeline of approximately 70 new molecular entities. Prior to Lilly, Dr. Paul served as scientific director of the National Institute of Mental Health. He has also served as medical director in the Commissioned Corps of the U.S. Public Health Service. Dr. Paul has authored or co-authored more than 500 papers and book chapters. He is an elected Fellow of the American Association for the Advancement of Science and a member of the Institute of Medicine. He currently serves on the board or as a trustee of several organizations, including SAGE Therapeutics, Alnylam Pharmaceuticals, the Sigma Aldrich Company, and the Foundation for the National Institutes of Health. Dr. Paul holds a B.A. in Biology and Psychology from Tulane University and an M.S. and an M.D. from the Tulane University School of Medicine.

William Z. Potter, M.D., Ph.D., spent 25 years positions in Intramural positions at the National Institutes of Health (NIH), where his research focused on translational neuroscience. While at NIH, Dr. Potter was

widely published and appointed to many societies, committees, and Boards. This enabled him to develop a wide reputation as an expert in psychopharmacological sciences and championing the development of novel treatments for central nervous system (CNS) disorders. Dr. Potter left NIH in 1996 to accept a position as executive director for early clinical neuroscience at Lilly Research Labs, and in 2004 joined Merck Research Labs (MRL) as Vice President of clinical neuroscience and then translational neuroscience, a position from which he retired in 2011. His experience at Lilly and MRL in identifying, expanding, and developing methods of evaluating CNS effects of compounds in the human brain cover state-of-the-art approaches across multiple modalities. These include brain imaging and cerebrospinal fluid proteomics (plus metabolomics) as well as development of more sensitive clinical, psychophysiological, and performance measures allowing a range of novel targets to be tested in a manner which actually addresses the underlying hypotheses. Dr. Potter continues as an emeritus co-chair of the Neuroscience Steering Committee of the Foundation for the National Institutes of Health and serves as a senior advisor to the director of the National Institute of Mental Health, where he champions the position that more disciplined hypothesis testing of targets in humans through public/private partnerships is the best near-term approach to moving CNS drug development forward for important neurologic and psychiatric illnesses.

Arti Rai, J.D., Elvin R. Latty Professor of Law and co-director, Duke Law Center for Innovation Policy, is an internationally recognized expert in intellectual property (IP) law, administrative law, and health policy. Ms. Rai has also taught at Harvard, Yale, and the University of Pennsylvania law schools. Ms. Rai's research on IP law and policy in biotechnology, pharmaceuticals, and software has been funded by the National Institutes of Health, the Kauffman Foundation, and the Woodrow Wilson Center. She has published more than 50 articles, essays, and book chapters on IP law, administrative law, and health policy. Her publications have appeared in both peer-reviewed journals and law reviews, including *Science*, the *New England Journal of Medicine*, the *Journal of Legal Studies*, *Nature Biotechnology*, and the Columbia, Georgetown, and Northwestern law reviews. She is the editor of *Intellectual Property Law and Biotechnology: Critical Concepts* (Edward Elgar, 2011) and the co-author of a 2012 Kauffman Foundation monograph on cost-effective health care innovation. From 2009–2010, Ms. Rai served as the administrator of the Office of External Affairs at the U.S. Patent and Trademark

Office (USPTO). As external affairs administrator, Ms. Rai led policy analysis of the patent reform legislation that ultimately became the America Invents Act and worked to establish USPTO's Office of the Chief Economist. Prior to that time, she had served on President-Elect Obama's transition team reviewing the USPTO. Before entering academia, Ms. Rai clerked for the Honorable Marilyn Hall Patel of the U.S. District Court for the Northern District of California; was a litigation associate at Jenner & Block (doing patent litigation as well as other litigation); and was a litigator at the Federal Programs Branch of the U.S. Department of Justice's Civil Division. Ms. Rai regularly testifies before Congress and relevant administrative bodies on IP law and policy issues and regularly advises federal agencies on IP policy issues raised by the research that they fund. She is a member of the National Advisory Council for Human Genome Research and of an Expert Advisory Council to the Defense Advanced Projects Research Agency. Ms. Rai is a public member of the Administrative Conference of the United States, a member of the American Law Institute, and co-chair of the IP Committee of the Administrative Law Section of the American Bar Association. Ms. Rai is currently a member of the Institute of Medicine Committee on Strategies for Responsible Sharing of Clinical Trial Data and has served on, or as a reviewer for, numerous National Academy of Sciences committees. In 2011, Ms. Rai won the World Technology Network Award for Law. She graduated from Harvard College, magna cum laude, with a degree in Biochemistry and History (History and Science), attended Harvard Medical School for 1 year, and received her J.D., cum laude, from Harvard Law School.

Kiran Reddy, M.D., M.B.A., is senior director of corporate strategy at Biogen Idec. Prior to joining Biogen Idec, Dr. Reddy was principal and associate partner at Third Rock Ventures. He helped create and grow several Third Rock-backed companies, including SAGE Therapeutics, where he was interim chief operating officer and chief business officer, and Foundation Medicine, where he was interim head of operations. Dr. Reddy is a Board-certified neurologist who completed training at Massachusetts General Hospital and Brigham and Women's Hospital. He completed his B.S., M.D., and M.B.A. degrees at Georgetown University.

Robert Ring, Ph.D., currently serves as chief science officer (CSO) for Autism Speaks, a role he has held since 2013. Autism Speaks is a leading science and advocacy foundation founded in 2005, which has been re-

sponsible for funding more than $200 million in research into causes, prevention, and treatment of autism spectrum disorder (ASD). A neuroscientist by training, Dr. Ring is responsible for leading the science program at Autism Speaks, which is focused on "putting scientific breakthroughs to work for families." This program at Autism Speaks features a diverse portfolio of research investments targeting etiology and environmental science, medical research, public health, innovative technologies, and genomic discovery. As CSO, Dr. Ring has specifically helped launch the Autism Speaks signature genomics discovery program, MSSNG (also known as "Aut10K" program), which has partnered with Google to develop an unprecedented open-access database of genomic sequence information to support the autism research ecosystem. Dr. Ring joined Autism Speaks in 2011 as vice president and head of translational research. In this role, Dr. Ring was responsible for launching the foundation's innovative venture philanthropy arm Delivering Scientific Innovation for Autism (also known as "DELSIA"), which support entrepreneurs and early-stage companies developing products that address unmet needs of the ASD community. Dr. Ring played an instrumental role in organizing the first Autism Investment Conference, which continues to run as an annual event supporting the rapidly growing marketplace for new product and business development to serve the needs of the people with autism. Dr. Ring also leads a collaborative partnership with the Simons Foundation to form a new international brain banking network now known as Autism BrainNet. Dr. Ring was appointed in 2014 by then-Secretary Kathleen Sebelius to serve as a public member of the Interagency Autism Coordinating Committee, the federal advisory committee that coordinates all efforts within the Department of Health and Human Services concerning ASD. Prior to joining Autism Speaks, Dr. Ring served as senior director and head of the Autism Research Unit at Pfizer Worldwide Research and Development in Groton, Connecticut. There he led the first dedicated research group in the pharmaceutical industry focused specifically on the discovery and development of medicines for neurodevelopmental disorders, specifically ASDs. Prior to Pfizer, Dr. Ring worked for more than 10 years in psychiatric medicines discovery and development at Wyeth Research in Princeton, New Jersey. Dr. Ring holds separate adjunct faculty appointments in the Department of Psychiatry at Mount Sinai School of Medicine (New York) and the Department of Pharmacology and Physiology at Drexel University College of Medicine (Philadelphia). He holds a B.A. in both Fine Art and Biology (double major) from Westmont College in Santa Barbara, California, and

a Ph.D. in Molecular Neurobiology from City of Hope National Medical Center in Southern California.

Rhonda Robinson Beale, M.D., is a seasoned health care executive with more than 20 years of experience in health care systems, managed care, and quality improvement, with demonstrated accomplishments for both behavioral health and medical systems. Dr. Robinson Beale has worked as a chief medical officer/physician executive for behavioral and medical in her work with several large national and local health care organizations, such as Optum, a subsidiary within UnitedHealth Group, PacifiCare, Cigna, Blue Cross Blue Shield of Michigan, and Health Alliance Plan. She has also been involved with many national organizations as a subject matter expert, including the National Institute of Mental Health, the Institute of Medicine (IOM), National Quality Forum, American Psychiatric Association, American Psychological Association, American Society of Addiction Medicine, National Committee for Quality Assurance, and others. She is currently on the IOM Board on the Health of Select Populations and National Quality Forum Map for Dual Eligibles and Behavioral Health. Dr. Robinson Beale has been involved in influencing local and national legislation, particularly around Parity and the Affordable Care Act. She testified before the Senate's Health, Education, Labor and Pension Committee due to her work on the IOM study *Crossing the Quality Chasm*. Dr. Robinson Beale also has experience as a health plan administrator, hospital medical director, and as a capitated practice owner who delivered care to patients.

Michael Rogawski, M.D., Ph.D., is professor of neurology and member of the Center for Neuroscience at the University of California, Davis. He is immediate past president of the American Society for Experimental Neurotherapeutics, a professional organization dedicated to advancing the development of improved therapies for nervous system disorders. Until 2006, he was senior investigator and chief of the Epilepsy Research Section at the National Institute of Neurological Disorders and Stroke (NINDS). Dr. Rogawski's research encompasses cellular neurophysiological studies, animal models, and clinical trials of new treatments for seizures and epilepsy. Laboratory studies conducted by Dr. Rogawski on AMPA receptors and neurosteroids have been translated to new epilepsy treatment approaches. In recognition of his research contributions, Dr. Rogawski has received the National Institutes of Health Director's Award, the Epilepsy Research Award from the American Society for

Pharmacology and Experimental Therapeutics, and the Service Award from the American Epilepsy Society. He presented the British Pharmacological Society Lecture, the Killam Lecture of the Montreal Neurological Institute, and the American Epilepsy Society's William G. Lennox Lecture. Dr. Rogawski is a founder and was chief editor of *Epilepsy Currents*, the journal of the American Epilepsy Society, and he was associate editor of *Neurotherapeutics*, the journal of the American Society for Experimental Neurotherapeutics. He currently serves as a special government employee to the Food and Drug Administration. Dr. Rogawski received his B.A. from Amherst College and his M.D. and his Ph.D. (Pharmacology) from Yale University. After serving as a Post-Doctoral Fellow in the Laboratory of Neurophysiology, NINDS, he completed residency training in neurology at Johns Hopkins.

Benjamin Roin, J.D., is an assistant professor of technological innovation, entrepreneurship, and strategic management at the Massachusetts Institute of Technology Sloan School of Management. He is also an associate member of the Broad Institute. Mr. Roin's work focuses on entrepreneurship, intellectual property, and innovation policy. His primary areas of research are patent law, biopharmaceutical innovation, and government regulation of the pharmaceutical industry. He has written about the market-exclusivity protections available for old and repurposed drugs, the implications of the finite patent term and limited patent-term extensions for drug development strategy, public and private insurer reimbursement policies, and Hatch-Waxman litigation. In 2013, he received the Kauffman/iHEA Award for Health Care Entrepreneurship and Innovation Research (along with Eric Budish and Heidi Williams). In addition to his academic research, he currently works with the National Health Council and the Multi-Regional Clinical Trial Center on issues related to patent law, Food and Drug Administration law, clinical trial regulations, and pharmaceutical innovation policy. Prior to joining the Sloan faculty in 2014, Roin was the Hieken Assistant Professor of Patent Law at Harvard Law School, where he taught courses on patent law, trade secrecy, and torts. Before joining the Harvard Law School faculty in 2008, he was an Academic Fellow at the Petrie-Flom Center at Harvard Law School, and clerked for Judge Michael McConnell on the U.S. Court of Appeals for the Tenth Circuit. He received his B.A. from Amherst College and his J.D. from Harvard Law School.

Edward F. Rover, J.D., is the chair, president, and CEO of the Charles A. Dana Foundation and of the Dana Alliance for Brain Initiatives, private philanthropic organizations committed to advancing brain research and to educating the public in a responsible manner about the potential of research to (1) develop a better understanding of the brain and its functions; (2) speed the discovery of treatments for brain disorders; and (3) combat the stigma of brain disorders through education. The Foundation, founded in 1950, works to achieve its goals through grants to institutions engaged in innovative neuroscience research and through public outreach efforts. Mr. Rover has practiced law since 1964 at White & Case LLP, currently as Of Counsel. He has served as a Trustee of numerous charitable organizations.

Katie Sale is the executive director of the American Brain Coalition (ABC), a nonprofit organization composed of some of the United States' leading professional neurological, psychological, and psychiatric associations and patient organizations. ABC seeks to advance the understanding of the functions of the brain and to reduce the burden of brain disorders through public advocacy. Ms. Sale has been executive director since ABC was incorporated in 2004. She initiated its Board procedure, bylaws, standard operating procedures, website, and media relations and marketing materials. She also established the ABC Board and committees. She has also secured the ABC membership, which has grown from 5 founding members to more than 90 member organizations. Ms. Sale provides executive leadership over the administration and manages its daily operations to ensure strong integration among all programs and advocacy activities. She provides broad guidance on operations and policy implementation. Ms. Sale participates with the Board in planning and establishing program policies, objectives, and priorities as well as directing the development and implementation of ABC's strategic action plans. Ms. Sale services the needs of ABC's membership, composed of patients, families, physicians, clinicians, industry, and government agencies. She has nearly 20 years of experience in nonprofit administration. Prior to joining ABC, she served as the senior director for planning and membership for the Society for Neuroscience. In this role, Ms. Sale coordinated the governance activities for the Society, supported its Council-driven strategic planning effort, supervised and serviced its membership and chapters, and managed the functions of the executive director's office. Ms. Sale received her B.S. in Speech Communications

with a Public Relations concentration and a minor in Human Relations from St. Cloud State University in Minnesota.

Andrew Sperling, J.D., M.A., is the director of federal legislative advocacy for the National Alliance on Mental Illness (NAMI). In this position, he leads NAMI's legislative advocacy initiatives in Congress and before federal agencies. Mr. Sperling works on issues affecting the mental health community with a focus on improving the lives of people with severe mental illnesses. Since 1994, Mr. Sperling has also served as co-chair of the Consortium for Citizens with Disabilities Housing Task Force. Prior to joining NAMI, Mr. Sperling held the position of deputy director of government relations for the National Community Mental Healthcare Council and was a legislative assistant for U.S. Representative Dick Swett (D-NH). Mr. Sperling earned his B.A. from Tulane University. He received an M.A. from George Washington University and a J.D. from the Franklin Pierce Law Center.

Maike Stenull, M.B.A., is the senior director, strategic projects and transformational leadership at the Office of the Chief Medical Officer at Johnson & Johnson (J&J). Ms. Stenull leads and manages transformational cross-sector, cross-functional initiatives that are integral to the operational effectiveness objectives. She is responsible for driving process, content, and business impact for large, complex transformational projects. Ms. Stenull has responsibility for J&J's Research & Development (R&D) Management Committee as the decision support lead. She is also the co-lead on the Global Alzheimer's Platform workstream focused on alternative finance options. Previously, she served as finance controller of the Neuroscience Therapeutic Area within Janssen R&D. Ms. Stenull has more than 20 years of cross-sector, cross-regional business experience within J&J. She has worked in medical devices and diagnostics, consumer and pharma, in various European countries and the United States. Ms. Stenull holds an M.B.A. from the Wirtschaftsakademie Hamburg in Germany. She is also a certified Six Sigma Black Belt (Process Excellence).

Paul Summergrad, M.D., is the Dr. Frances S. Arkin Professor and Chair of the Department of Psychiatry and professor of medicine at the Tufts University School of Medicine and psychiatrist-in-chief of Tufts Medical Center. Dr. Summergrad is the president of the American Psychiatric Association. He also serves as chair, interim president, and CEO

of the Tufts Medical Center Physicians Organization and as a member of the Tufts Medical Center Board of Trustees. Prior to his arrival at Tufts in 2004, he served at the Massachusetts General Hospital (MGH) and Harvard Medical School, where he was associate professor of psychiatry and chief of inpatient psychiatric services at MGH. He also served as network director of the Partners Psychiatry & Mental Health System. In that role he also served as psychiatrist-in-chief of the North Shore Medical Center, where he was executive vice president for medical affairs and chief medical officer and a member of the Partners Executive Committee. A 1978, Alpha Omega Alpha graduate of the School of Medicine at the State University of New York of Buffalo, he trained in internal medicine at the Boston City Hospital from 1978–1981 and in psychiatry at the Massachusetts General Hospital from 1982–1985 where he was chief resident. He graduated from psychoanalytic training at the Boston Psychoanalytic Society and Institute, where he is a member. He is Board certified in internal medicine, psychiatry, psychosomatic medicine, and geriatric psychiatry. Dr. Summergrad has published extensively on the history and development of psychiatry, medical psychiatry, neuropsychiatry, psychopharmacology, and strategic planning in academic medical centers, including editing with Roger Kathol the recent book *Integrated Care in Psychiatry*. His research focuses on mood disorders, medical-psychiatric illness, and health system design. He is a Distinguished Fellow of the American Psychiatric Association and a Fellow of both the American College of Psychiatrists and the American College of Physicians. In addition to his clinical, academic, and administrative roles, Dr. Summergrad is immediate past president of the American Association of Chairs of Departments of Psychiatry and immediate past chair of the American Hospital Association Governing Council for Psychiatry and Substance Abuse Services. He served as the chair of the American Psychiatric Association (APA) Board of Trustees Ad Hoc Workgroup on the Role of Psychiatry in Healthcare Reform and served as a member of the APA Board of Trustees DSM-5 Scientific Review Committee. He has served as a member of the Finance and Budget Committee, the Assembly of the Steering Committee on Practice Guidelines, and the Council on Medical Education. He is a past president of the Massachusetts Psychiatric Society and the American Association of General Hospital Psychiatrists.

William Thies, Ph.D., is Senior Scientist in Residence with the Alzheimer's Association. Dr. Thies is formerly chief medical and scientific officer of the Alzheimer's Association, where he oversaw the world's

largest private, nonprofit Alzheimer's disease research grants program. During his tenure, the organization's annual grant budget more than doubled. Since its inception in 1982, the Alzheimer's Association grants program committed more than $300 million for Alzheimer's disease research. Dr. Thies was instrumental in bringing the Alzheimer's Association International Conference (AAIC) under the umbrella of Association activities. AAIC is the world's largest gathering of Alzheimer and dementia researchers, regularly drawing more than 5,000 attendees. In addition, Dr. Thies played a key role in launching the peer-reviewed journal *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* and the Association's Research Roundtable. The Roundtable provides a unique forum for senior scientists from the pharmaceutical industry, biotech, imaging, academia, the National Institutes of Health, and regulatory agencies to discuss common issues and obstacles in Alzheimer's disease research and drug development. Before joining the Alzheimer's Association, Dr. Thies was a director and senior scientist at the American Heart Association. He previously held faculty positions at Indiana University and the University of Pittsburgh.

Peter Ubel, M.D., is a physician and behavioral scientist whose research and writing explores how people make decisions related to health and health care. He is the Madge and Dennis T. McLawhorn University Professor of Business, Public Policy, and Medicine at Duke University. His research explores the role of values and preferences in health care decision making, from decisions at the bedside to policy decisions. He uses the tools of decision psychology and behavioral economics to explore topics such as informed consent, shared decision making, and health care cost containment. He has authored more than 250 academic publications, the majority of which involve empirical explorations of decision psychology as it pertains to health care. He has also written for the *New York Times*, the *Los Angeles Times*, the *Atlantic*, and the *New Yorker*. Dr. Ubel is a regular contributor at *Forbes*. His books include *Pricing Life* (MIT Press, 2000), *Free Market Madness* (Harvard Business Press, 2009), and *Critical Decisions* (HarperCollins, 2012).

George Vradenburg, J.D., is the chair and co-founder of USAgainstAlzheimer's, an education and advocacy campaign committed to mobilizing America to stop Alzheimer's, and convener of the Global CEO Initiative (CEOi) on Alzheimer's. Through his USA2 work, he has brought together powerful voices to escalate the fight against Alzheimer's, as co-convener

of Leaders Engaged on Alzheimer's Disease (LEAD) (a network of major Alzheimer's-serving organizations from the not-for-profit, foundation, academic, corporate, and government sectors) and as convener of the Global CEO Initiative Against Alzheimer's (a public–private initiative to link public, private, and nongovernmental organization efforts to implement the National Alzheimer's Goal to stop Alzheimer's by 2025). He was named by former Health and Human Services Secretary Kathleen Sebelius to serve on the National Alzheimer's Advisory Council to advise on the first-of-its-kind National Alzheimer's Strategic Plan. Among other efforts, Mr. Vradenburg has testified before Congress about the global Alzheimer's pandemic; has conceived and supported the Alzheimer's Study Group; and, through the Vradenburg Foundation, has supported the Alzheimer's disease International World Alzheimer's Reports and the National Institutes of Health's Global Alzheimer's Research Summit. Mr. Vradenburg was appointed to the bipartisan Commission on Long-Term Care in 2013. Before his retirement, he served in senior executive positions at AOL/Time Warner, Fox, and CBS. He is a member of the Council on Foreign Relations and the Economic Club of Washington. Mr. Vradenburg received his B.A. from Oberlin College, magna cum laude, and his J.D. from Harvard Law School, cum laude.

David Wholley, M.Phil., manages the Research Partnerships Division of the Foundation for the National Institutes of Health. Programs under the Research Partnerships Division include The Biomarkers Consortium, Accelerating Medicines Partnership, and LungMAP, a multidrug "master protocol" trial in squamous cell lung cancer. He has also served as director of the Genetic Association Information Network, a public–private partnership dedicated to helping discover the genetic basis of common disease, and led the development of a major public–private partnership in drug safety with the biopharmaceutical industry and Food and Drug Administration. Prior to joining the Foundation in 2006, Mr. Wholley's career spanned nearly 25 years in health care technology management, including extensive experience in product development, sales, marketing, corporate strategy, and partnership and project development. Mr. Wholley has held senior management roles in several venture-funded technology start-up companies, including head of global marketing and development for First Genetic Trust, Inc., which developed software for large-scale, collaborative genetic research and personalized medicine. During a 16-year career at IBM, he co-led the corporate strategy team that guided IBM's formation of its Life Sciences industry organization. Mr. Wholley

holds an M.Phil. from Rutgers University and a Certificate in Business Administration from the Stern School of Business at New York University.

Janet Woodcock, M.D., is director of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA). Dr. Woodcock first joined CDER in 1994 and FDA in 1986. From 2005 until 2008, she served as FDA's commissioner, holding several positions, including deputy commissioner and chief medical officer, deputy commissioner for operations, and chief operating officer. Her responsibilities involved oversight of various aspects of scientific and medical regulatory operations. Before joining CDER, Dr. Woodcock served as director, Office of Therapeutics Research and Review, and acting deputy director in FDA's Center for Biologics Evaluation and Research. Dr. Woodcock received her M.D. from Northwestern University Feinberg School of Medicine and completed further training and held teaching appointments at the Pennsylvania State University and the University of California, San Francisco.