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Perspective

Medicines for the Mind: Policy-Based "Pull" Incentives for Creating Breakthrough CNS Drugs

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Several large pharmaceutical companies have selectively downsized their neuroscience research divisions, reflecting a growing view that developing drugs to treat brain diseases is more difficult and often more time-consuming and expensive than developing drugs for other therapeutic areas, and thus represents a weak area for investment. These withdrawals reduce global neuroscience translational capabilities and pose a serious challenge to society's interests in ameliorating the impact of nervous system diseases. While the path forward ultimately lies in improving understandings of disease mechanisms, many promising therapeutic approaches have already been identified, and rebalancing the underlying risk/reward calculus could help keep companies engaged in making CNS drugs. One way to do this that would not require upfront funding is to change the policies that regulate market returns for the most-needed breakthrough drugs. The broader neuroscience community including clinicians and patients should convene to develop and advocate for such policy changes.

We need to act now to stem an untimely flow of industry research resources away from the fight against diseases of the nervous system.

The combined human and economic impact of these diseases is stunning. It is estimated that nearly 100 million Americans suffer from nervous system disorders, resulting in an annual economic cost of over $760 billion (Society for Neuroscience, 2014). Data from across the Atlantic suggest that these figures may be too low, as in 2010 brain disorders affected 38% of Europeans and accounted for about one-third of total disease burden and health-related direct and indirect expenses, with mood disorders, dementia, psychotic disorders, anxiety disorders, and addiction proving especially costly (Gustavsson et al., 2011). Worldwide, stroke is the second-leading cause of death, and nervous system disorders account for 12 of the top 20 causes of years lived with disability (Vos et al., 2012); furthermore, two additional top-20-ranking causes, falls and road injury, often reflect brain disorders such as substance abuse, sensory-motor impairment, or sleep disturbances.

Amelioration of this terrible impact awaits the development of more effective therapies and prevention strategies. Fortunately, understanding of brain biology and brain disease mechanisms continues to advance apace, leading United States political and scientific leadership to call last year for a coordinated national push in brain research, and the European Commission to launch a large-scale Human Brain Project. Unfortunately, several large pharmaceutical companies have recently withdrawn from the neuroscience research, leading to a substantial decline in capacity and translational capabilities at this moment of need and opportunity.

The Problem Statement

It is difficult to assess the precise extent of this decline, although it has been recognized recurrently in news pieces and the scientific literature (e.g., Miller, 2010; Nutt, 2011; Insel and Landis, 2013; Wegener and Rujescu, 2013). While several pharmaceutical companies remain heavily engaged in neuroscience research, six of the ten largest pharmaceutical companies (on the basis of 2013 global sales) have sharply reduced their efforts; these same companies held four of the five largest neurological/psychiatric disease ("CNS") drug pipelines in 2009 (N. Wendel and C.-P. Milne, Tufts Center for the Study of Drug Development, personal communication). GlaxoSmithKline and AstraZeneca have nearly closed their global neuroscience research divisions. Merck, Pfizer, and Sanofi-Aventis have each closed research facilities and consolidated teams. Novartis announced the closure of its main conventional neuroscience research facility in Basel at the end of 2011 (although a new division working on the genetics of psychiatric and cognitive disorders was recently opened in Cambridge). In addition, a seventh giant pharmaceutical

Table 1. CNS Program Portfolios in Large Pharma: 2009 versus 2014

	2009	2014
Total Programs	267	129
Abbott/AbbVie	17	10
AstraZeneca	21	7
Bristol-Myers Squibb	12	2
GlaxoSmithKline	40	14
Johnson & Johnson	18	17
Lilly	16	9
Merck/Schering-Plough	32	7
Novartis	14	15
Pfizer/Wyeth	46	15
Roche/Genentech	22	21
Sanofi/Genzyme	29	12

Total number of discovery, preclinical, and clinical drug development programs addressing neurology or psychiatry disease targets, visible from publicly available sources including SEC filings, investor briefings, and company websites.

company, Bristol-Myers Squibb, announced plans at the end of 2013 to terminate discovery work in neuroscience, with the exception of one Alzheimer's disease program. A count of publically visible clinical CNS programs in 11 large pharmaceutical companies in 2014 revealed half the number that were visible in 2009 (Table 1; H. Tracy, personal communication).

Taken together, these announced withdrawals signify the loss of sizeable research resources from the neuroscience field, with full impact likely still ahead as existing product pipelines run down. An approximate vertical scale is provided by data indicating that in 2002 (the last year that the Pharmaceutical Research and Manufacturers of America [PhRMA] reported research expenditures by therapeutic area), member large pharmaceutical companies invested $5.3 billion in CNS drug research and development (R&D), comparable to the $5.1 billion invested in neurosciences by NIH (Dorsey et al., 2006) and about 17% of total PhRMA research spending. Furthermore, while industry supports research activities across the entire spectrum from basic molecular discovery to clinical trials, large companies have long been the dominant sponsor of the advanced medicinal chemistry often needed to optimize a lead molecule into a practical drug, as well as the large-scale multicenter phase 3 clinical trials required to establish drug safety and efficacy in many disease areas. Their withdrawals will particularly impair these critical efforts—analogous to losing the anchor leg runners in relay races—and are likely to ripple deep into the greater ecosystem supporting drug development. Corporate support for academic societies and scientific meetings in the neuroscience area has already palpably faltered, a small, but impactful, change given the role that industry-sponsored "no strings" workshops and lectures play in keeping scientists informed and catalyzing collaborations.

So far, funding for CNS biotechnology companies from venture capital and other seed investors continues to be healthy (Korieth, 2014; Ford and Nelsen, 2014), but continuing large-company withdrawals from neuroscience may threaten this vital source of innovation by reducing potential partnership opportunities and exit strategies, and thus the attractiveness of the sector for investment. An increasing number of new drugs are being brought to market by smaller companies (Munos, 2009), but it would be overly optimistic to imagine that this bright spot can fully compensate for declining large-company commitments to neuroscience, as (1) smaller companies tend to focus selectively in areas such as orphan indications that are approachable with relatively inexpensive clinical trials, and (2) small-company successes emerge stochastically from a massive company base (> 73,000 bioscience companies, > 3,000 drug companies in the United States in 2012; Battelle/BIO, 2014) dependent on ecosystem resources.

Making CNS Drugs Is Difficult, but Doable

Industry cutbacks in neuroscience research in part reflect the growing challenges facing pharmaceutical drug development in general, as overall success rates have fallen, and the fully loaded cost to discover and develop a new drug has ascended to the range of $1.8–$3.9 billion (Kola, 2008; Munos, 2009; Khanna, 2012). But both PhRMA and total industry research investments (PhRMA, 2014; Research America, 2014) have held up, leveling in recent years around $50 billion and $69 billion, respectively. What appears to be the main driver of the specific departures of companies from neuroscience research is deterioration in sector risk/reward calculus. The neuroscience sector is now widely considered to be less attractive than most other therapeutic sectors for research investment due to higher financial risk, despite potentially large markets and compelling societal benefits (Miller, 2010). This higher risk reflects a lower probability of candidate drug development success (see below and elsewhere in this issue), coupled with relatively high program costs and longer-than-average clinical trials and regulatory agency review times driven by the complexity of clinical development. For all new chemical entities approved by the FDA between 2003 and 2012, neurology and psychiatry drugs required a mean review time (date of NDA submission to approval) of 24.5 months, compared to 17.7 months for cardiovascular drugs, 12.5 months for immunology/infectious disease drugs, and 8.1 months for oncology drugs (D. Michelson and S. Posey Norris, personal communication). The total clinical trial plus FDA review time for CNS drugs approved between 1996 and 2010 averaged 32 months (35%) longer than for non-CNS drugs (Tufts Center for the Study of Drug Development, 2012). This additional time erodes remaining patent life, resulting in shortened periods of market protection prior to the entry of generic drug competition (see below).

The unfavorable calculus around neuroscience drug development has emerged in the wake of a series of recent pipeline disappointments, and should not be viewed as categorical. Rather, it lies on an estimation cusp, as reflected in the continuing commitment of several large pharmaceutical companies to the sector. Not long ago, neuroscience was considered to be a cornerstone area by most large companies. Between 1995 and 2002 (the last year that the PhRMA reported research expenditures by therapeutic area), PhRMA member investment in the neuroscience research doubled from $2.5 billion to the $5.3 billion noted above (Dorsey et al., 2006). An analysis of candidate

drugs first tested in human between 1993 and 2004 revealed a regulatory success rate of 8.2% for CNS drugs—not so different from the success rate for cardiovascular drugs (8.7%), gastrointestinal/metabolic drugs (9.4%), or respiratory drugs (9.9%) (DiMasi et al., 2010), but any amount lower, especially compounded by reduced market protection time, can constitute a significant investment disincentive in the absence of counterbalancing advantages.

Brain biology is indisputably complex. Developing first-in-class CNS drugs faces multiple serious hurdles, including most importantly a still-limited knowledge of disease mechanisms (Insel and Landis, 2013; also see Pankevich et al., 2014 [this issue of *Neuron*]), but complete mechanistic understandings are not required to achieve major clinical impact (consider for example, L-dopa, SSRIs, benzodiazepines, or various anticonvulsants). As attested to by the current literature as well as the vigor of the CNS biotechnology company sector, enough is known about the pathogenesis of multiple CNS diseases to generate a substantial number of reasonable hypotheses and therapeutic approaches, ready for testing in man. In fact, only clinical testing will suffice to reject or validate these hypotheses, given the prominent limitations of animal models of CNS disease. Promising new therapeutic fronts supported by early human data are now opening even in disorders as profound, and yet mysterious, as autism spectrum disorders or depression (Canitano, 2014; McGirr et al., 2014). Those of us with experience working in pharmaceutical company laboratories (D.W.C., A.P., S.P., and W.P.) can recall multiple examples of potentially important CNS programs that did not gain the internal resources needed to move forward because they fell below a corporate action threshold defined by projected return on investment. A distinguished working group of the Advisory Committee to the NIH Director has just assessed the state of neuroscience research, and concluded that the present is "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" (BRAIN Working Group Report to the Advisory Committee to the Director, NIH, 2014). We owe it to the many people affected by nervous system diseases to keep taking our best therapeutic shots now, and to ensure that translational capabilities remain intact for the discoveries that lie ahead.

A Call to Action: Improving Risk/Reward Calculus

In the longer run, the most powerful way to ensure industry engagement in neuroscience, as with all therapeutic areas, is to reduce risk by finding more effective and efficient ways to develop new therapeutic agents. Front and center is the need to continue to advance understandings of disease mechanisms and drug toxicity through basic and applied research, with attendant implications for the desirability of enhancing research funding, coordination, infrastructure, and workforce training. Specifically needed are better ways to validate therapeutic targets preclinically, to predict on- and off-target toxicities, and to bring a larger number of candidate approaches into less expensive exploratory clinical testing than historically achieved (Choi, 2002; Paul et al., 2010). Building such improved early clinical development pathways will likely require prospectively identifying biomarkers, establishing trial networks such as NIH's NeuroNEXT, and deploying adaptive trial designs. Costs and risks can also be reduced through newer approaches involving open sourcing, data sharing, repurposing drugs for novel indications, precompetitive industry consortia, and public-private research partnerships (Kola, 2008; Munos, 2009; Paul et al., 2010; Manji et al., 2014).

As these risk reduction efforts are receiving attention elsewhere, the present paper will focus on the synergistic goal of reward sufficiency. The former are push incentives that lower drug research costs and improve success probabilities; the latter are pull incentives that increase the market benefits of success. By providing greater and more reliable financial returns for the successful development of CNS drugs, pull incentives would provide an economic rationale that would help keep industry in that business.

To maximize rationale and feasibility, we will center our considerations on pull incentives that are potentially achievable here and now in the United States, apply only to the development of innovative drugs addressing major unmet needs, and will not require significant upfront public funding, i.e., can be implemented through policy and regulatory changes alone. Thus, we will not discuss here possible pull incentives like advance market commitments, that would involve guaranteeing minimum revenue levels for drugs meeting certain specifications; or prizes, that would need to be awarded at intermediate stages of drug development to be meaningful (a prize awarded upon FDA approval would likely be dwarfed by market revenues). Drug development and large pharmaceutical companies are global enterprises, but America is the world's largest pharmaceutical market and hence a reasonable and influential place to initiate change. Rigorous restriction to breakthrough, high-medical-impact drugs will preclude unintended use of the incentives to provide commercial benefits out of proportion to societal benefits, for example, by supporting the development and marketing of drugs which are similar to existing drugs. And an "upfront budget-neutral" limitation will lower the bar to action by eliminating the dilemma of competition with many worthy calls on public resources (including the compelling case for increasing basic scientific research funding).

Of course, there is no free lunch. Policy changes that increase the financial returns associated with successful neuroscience drug development will do so by increasing drug costs. However, these downstream expenses will likely be more than counterbalanced by the health benefits and healthcare cost savings produced by these drugs (Kleinke, 2001; Lichtenberg, 1996), as is well illustrated by the impact of antiretroviral therapies for HIV infections (Gonzalo et al., 2009) or the calculation that a treatment breakthrough in 2015 capable of delaying the age of onset of Alzheimer's disease by only five years would save $447 billion in direct care costs by 2050 (Alzheimer's Association 2010).

More Than You Ever Wanted to Know About Market Protection for New Drugs

Before discussing possible specific policy-based pull incentives, it is useful to briefly outline the extant basis for the market protection of new drugs in the United States and several precedents for policy-based pull approaches to incentivizing commercial engagement in neglected therapeutic sectors (Figure 1). We

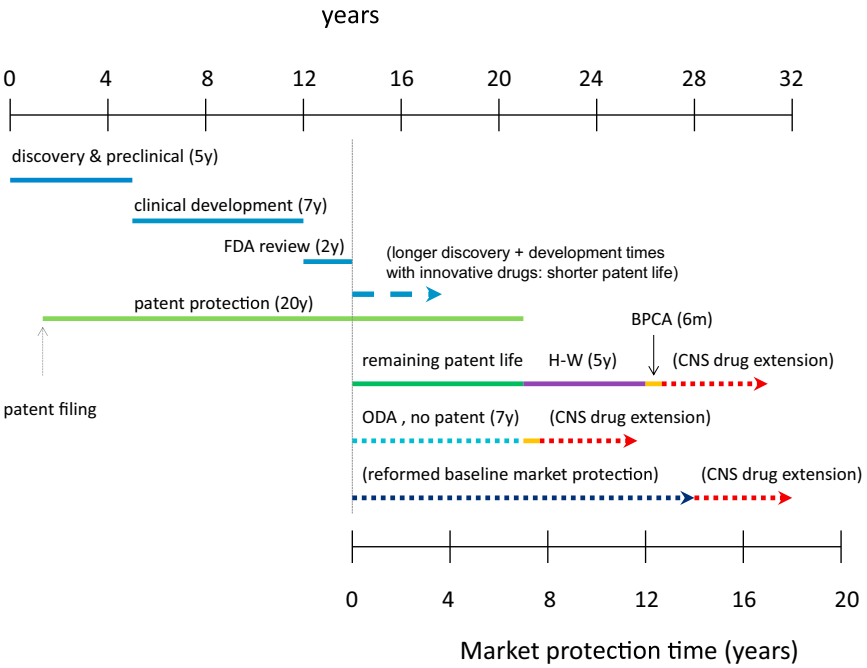

Figure 1. Drug Development and Market Protection Timelines for a Novel Drug

The upper part of the diagram illustrates a typical drug discovery and development program timeline, with 24 months spent in FDA review (the mean review time for a CNS drug–see text). Patent applications, for example, covering the drug's chemical structure, are usually filed early in the discovery process, prior to preclinical studies (examining metabolism, pharmacokinetics, and toxicity) and clinical trials.

The lower part of the diagram illustrates market protection timelines. By the time the drug is brought to market, a majority of relevant 20-year patent term(s) have usually expired, but up to 5 years of a key patent's life can be restored by Hatch-Waxman (H-W, purple bar), with possibly another 6 months of market exclusivity provided by BPCA (orange bar). As noted in the text, the longer development times required by innovative or preventive drugs can further substantially run down the patent clock, rendering market protection time commercially unviable. The additional term of market protection for breakthrough CNS drugs proposed here (red dashed lines) would extend the market protection provided currently (by existing patent law + H-W patent life restoration ± BPCA, or by ODA ± BPCA for an orphan drug lacking meaningful patent protection), or in the future (by a reformed market protection policy providing a fixed term of protection to breakthrough, high-medical-impact drugs in all therapeutic areas, timed to begin with the date of FDA approval).

recognize that the topic of market protections rarely competes for the consciousness of neuroscientists, but believe that it deserves the community's attention at this time.

Innovative new small-molecule drugs are typically protected by patents of varying strength and effectiveness, with a nominal term of 20 years from date of filing. Patents on a medicine's active ingredient usually provide much stronger protection from competition than patents covering clinical use or how the medicine is formulated into a dosage form. For the most important forms of patent protection, patent filing typically occurs well prior to the start of clinical development, and thus much of their term is consumed before the medicine can be marketed.

On average, it takes a research-based pharmaceutical company 11–14 years to bring a new drug to market, with a majority of this time spent in phase 1 through phase 3 human clinical trials (Paul et al., 2010). New drugs would almost invariably face generic drug competition long before they had gained adequate revenues to achieve commercial success, were it not for the Drug Price Competition and Patent Term Restoration Act of 1984 (commonly referred to as the Hatch-Waxman Act), which adds up to 5 years back to the patent clock (up to a maximum of 14 years after FDA approval) to help compensate for time spent in clinical trials and regulatory agency consideration. Hatch-Waxman also facilitates generic competition following patent expiry, permitting a manufacturer of a generic drug to gain market entry after demonstrating bioequivalence to a patented drug, and incentivizing patent challenges. Notably, even with patent term restoration, only 20% of marketed drugs achieve earnings greater than their own development costs (Vernon et al., 2010).

The pioneering precedent for a policy-based pull incentive aimed at attracting industry to a neglected therapeutic sector was provided by the Orphan Drug Act (ODA) of 1983. The ODA contained several provisions to encourage industry to target rare diseases (defined as affecting < 200,000 Americans) lacking intrinsic market appeal, including tax credits and grants to ameliorate development costs, a fast-track regulatory pathway, and a 7-year period of registration exclusivity for the "orphan" indication of use, independent of the medicine's patent status, that begins upon FDA approval. This last pull incentive, which assures a minimum duration of market protection for single-indication orphan medicines, was originally intended to compensate for a lack of strong patent protection. However, before the ODA's 7-year, indication-specific exclusivity could be tested as an incentive, the Act was largely superseded by the Hatch-Waxman Act that effectively afforded all new chemical entity drugs a similar or greater protection period for all indications. Nonetheless, the ODA by any measure has been a success; between 1983 and 2012, more than 400 orphan-designated medicines representing 447 separate indications were approved, compared to only 10 over the prior decade (PhRMA, 2013). Some concerns have arisen about use of the ODA to support drugs with high prices, even amid blockbuster sales (> $1 billion per year) (Murphy et al., 2012) or extensive off-label use.

A second precedent was provided by the Best Pharmaceuticals for Children Act (BPCA) of 2002, which rewarded companies for studying the pediatric efficacy of agents already approved for adult use by providing for a 6-month extension of market exclusivity (often called "pediatric exclusivity"). While BPCA has contributed to advancing pediatric medicine, its incentive value is variable, determined by adult market profiles unrelated to the extent of pediatric benefits, and can thus end up inefficient or insufficient. In some cases, BPCA has created windfall financial returns by increasing sales to adults without providing

commensurate pediatric benefits; in others, its benefits have fallen short of the costs of meritorious pediatric study.

A third and especially relevant precedent is provided by the "Generating Antibiotic Incentives Now" (GAIN) Act of 2012. The enormous public threat posed by the emergence of antibiotic-resistant bacteria has not been adequately met by industry attention to developing new antibiotics, in part due to scientific difficulty, but also in part due to relatively weak projected market returns, reflecting typically small numbers of affected individuals, short durations of therapy, and a history of modest pricing and reimbursement for antibiotic drugs. In response, the Infectious Diseases Society of America (IDSA), representing more than 7,500 clinicians and researchers, mobilized support for policy change, beginning with the publication of a white paper in 2004 entitled "Bad Bugs, No Drugs" (Infectious Diseases Society of America, 2004). This influential paper sketched a wide array of possible push and pull incentives of varying feasibilities (Kesselheim and Outterson, 2010), and was followed by advocacy efforts and the publication of additional white papers. IDSA actions, augmented by the voices of the European Centre for Disease Protection, the World Health Organization, and the World Economic Forum, culminated in passage of the GAIN Act.

The GAIN Act granted qualified new antibiotic agents a new pull incentive: an additional 5 years (5.5 years if paired with a diagnostic test) of market exclusivity on top of Hatch-Waxman's baseline 5-year new chemical entity data package protection, or ODA's 7-year registration exclusivity—as well as a favored regulatory pathway to approval. Time will tell if the GAIN Act is sufficient to rekindle industry attention on antibiotic drug development, although early indications suggest that it may fall short (Ambrose, 2011). Even maximized (added on top of ODA plus BPCA plus a companion diagnostic test), GAIN provides only 13 years of market exclusivity. This protection can be better than that provided by Hatch-Waxman in being independent of patents, but its duration is operationally similar to that often available under Hatch-Waxman.

Policy-Based Remedies: Two Caveats and Three Suggested Tiers

In considering policy initiatives to create greater pull incentives for CNS drugs, we attended to two important and related caveats. First, the existing market protection landscape should not be regarded as fixed. Current protections for conventional small-molecule drugs constitute a complex patchwork of mixed protections, combining patent law, patent life restoration under Hatch-Waxman, and any applicable market exclusivity protections provided by the ODA, BPCA, or GAIN Act. While Hatch-Waxman has done much to promote a balance between drug innovation and drug costs, as well as the respective interests of research-based and generic pharmaceutical companies, its dependence on patent law and the patent clock is a well-recognized core weakness. The clinical merit of a drug and the strength or length of the patent protection that it may have are not necessarily correlated (Roin, 2009); furthermore, the fixed patent clock coupled with the 5/14-year Hatch-Waxman caps on patent life restoration discourages the development of therapeutics requiring lengthy clinical trials to establish efficacy, regardless of medical desirability. This defect tends to systematically disadvantage drugs targeting chronic or early-stage diseases, disease prevention drugs, and breakthrough drugs in general, since opening up a new therapeutic paradigm typically requires more exploratory work than fast following an established clinical experimental pathway. It is already common for drug development times to outstrip patent term restoration possibilities. For all drugs losing market protection in 2011–2012, the average market exclusivity period was 12.9 years (Grabowski et al., 2014), meaningfully less than the theoretical maximum protection time of 14 years (14.5 years if the BPCA applies) afforded under Hatch-Waxman (despite averaging in a number of follow-on drugs). An example of bias toward late acute interventions and away from medically desirable early-stage or preventive treatments can be seen in the currently commercially favored cancer field (Budish et al., 2013).

A second caveat is that advocacy for incentivizing CNS drug development should not be framed as a zero-sum competition between neuroscience and other therapeutic areas. Rather, the neuroscience community should ally with other communities to use the occurrence of commercial withdrawal from neuroscience to exemplify the need to reform the existing system of drug protections, assuring an adequate period of market protection that would begin upon regulatory approval for all innovative drugs fulfilling unmet medical needs. While at the moment CNS and antibiotic drug development would particularly benefit from enhanced incentives, neither area required such in the past, and a decade from now, it may be other areas that need a specific boost. Diseases in all therapeutic areas have the capability to kill or devastate quality of life. The entire biomedical community should support the institution of a flexible incentive structure, capable of maintaining an optimal alignment of the market protection system with society's changing medical needs.

With these precedents and caveats in mind, we propose that three tiers of policy changes be considered, starting with across-the-board changes and then focusing on breakthrough, high-medical-impact CNS drugs (Figure 2).

Broad Market Protection Reform Recognizing Innovation

The first tier of change should seek to reform the current system of market protections to address the shortcomings noted above and elsewhere (e.g., Grabowski et al., 2011; Armitage, 2014). This will be a challenging undertaking, but a significant step in the right direction was taken recently with the passage of the Biologics Price Competition and Innovation (BPCI) Act of 2010, a component of the Patient Protection and Affordable Care Act, which provides new biological therapeutics with a straight 12 years of protection starting from the date of FDA approval (12.5 years with a BPCA pediatric extension) independent of patent status. During this protected time, a "biosimilar" competing product cannot reference the initial data package and is therefore denied a facilitated path to market entry. However, BPCI's approach to IP protection for biologics is fundamentally different from the patent-based approach that now dominantly protects new small-molecule drugs. This bifurcation makes no rational sense. Indeed as technology advances and it becomes possible to characterize and manufacture increasingly complex molecules with precision outside of living systems, distinctions between these classes may blur.

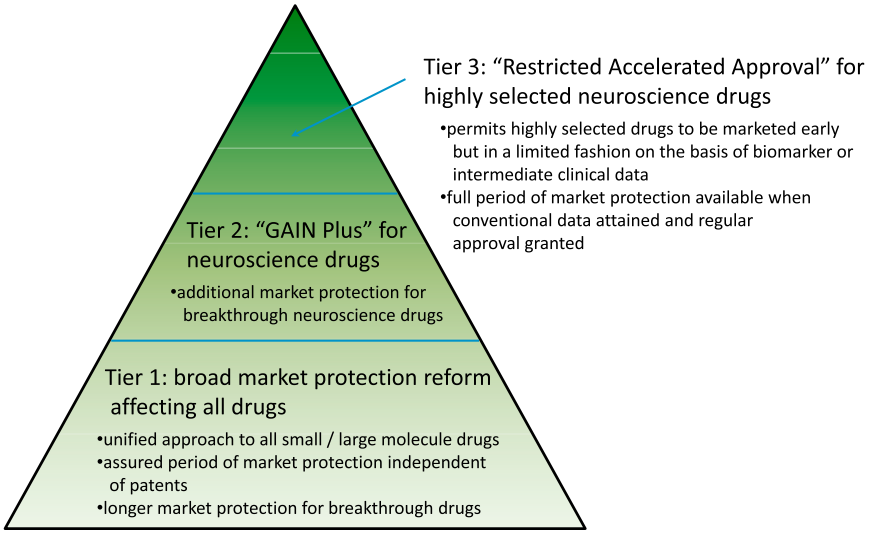

Figure 2. Proposed Three Tiers of Policy Changes to Incentivize Neuroscience Drug Development

Ascending tiers have progressively smaller scope, but larger incentive power. Ultimately Tier 2 could be absorbed into Tier 1 if Tier 1 incorporated the flexibility to accommodate dynamically changing market protection in therapeutic sectors as deemed desirable by policy makers.

We suggest that the goals of reform should be (1) to create a unified approach to market protection for drug therapies that would retain the balanced encouragement of the innovation-generic competition life cycle that has served society well to date, (2) to decouple market protection from obligate dependence on patent law and the patent clock, permitting innovative and valuable therapies to be developed regardless of patentability, and then to have an assured duration of market protection beginning upon FDA approval, regardless of time spent in development, and (3) to provide differentially greater market protection for truly meaningful innovation—breakthrough therapies addressing major unmet medical needs. Currently, the modest innovation inherent in developing a "me too" drug, which is a chemical modification away from existing molecules or is the *n*th drug in an already well-covered molecular class, receives the same patent-based protection as a drug that moves into uncharted therapeutic space and addresses a major unmet medical need (and the "me too" drug will likely have longer market protection, due to a quicker development path). Perhaps some merit-based supplemental market protection might additionally be awarded post marketing, to recognize achieved clinical performance and societal benefit and thus provide a general background incentive for companies to seek significant innovation. Furthermore, the mechanisms supporting #3 might incorporate sufficient flexibility to be able to accommodate sector-specific incentives when these are deemed necessary by policy makers. The authority for determining whether a given therapeutic agent is eligible for supplemental market protection would be logically vested in FDA, which might utilize objective metrics such as projected quality-adjusted life year benefits, as well as the advice of unconflicted outside experts and patient advocates along lines currently employed to arrive at approval decisions.

In an ideal world, one would replace the current patchwork of IP protections with a streamlined single policy more resistant than current policies to system-gaming legal maneuvers on the part of either research-based or generic companies. An attractive and likely more practical add-on approach is now being brought before Congress with the support of the National Health Council and patient advocacy organizations: the proposed Modernizing Our Drug and Diagnostic Evaluation and Regulatory Network (MODDERN) Cures Act. MODDERN Cures would sit on top of the existing protection system for both small-molecule and biological drugs, offering the sponsors of drugs determined to address unmet medical needs the option of a definitive protection period beginning with FDA approval, that would replace other protections and also end crisply (precluding the wrangling over applicable patents that often occurs today as market protection ends) to enable full generic competition (Armitage, 2014). We also note the conceptual framework provided by the European drug regulatory system, which accords a fixed period of combined data and market exclusivity to all new drugs beginning with European Medicines Agency approval, and an additional year of market protection for establishing a new therapeutic indication and bringing significant clinical benefit over existing therapies.

"GAIN Plus" for Breakthrough, High-Impact CNS Drugs

On the likely assumption that it will be some time before the current system of market protections is reformed and has built-in capabilities to provide sector-specific boosts, the neuroscience community should follow the lead of the infectious diseases community and consider the near-term creation of a breakthrough CNS drug-specific pull incentive conceptually similar to that created by the GAIN Act (Figure 1). Case-by-case drug candidate eligibility for this additional incentive should be judged by the FDA and its outside advisors, and have a high bar, to ensure that the incentive is only applied to truly innovative drugs meeting major unmet medical needs. However, learning from the GAIN Act experience, we suggest that the CNS drug-specific extension of market protection should be additional to all other applicable protections, whether based on the patent term restoration granted by Hatch-Waxman, pediatric exclusivity, BPCI, ODA, or a new policy like MODDERN Cures. Alternatively, a CNS drug-specific, fixed period of combined patent restoration and data protection (e.g., 18–20 years) beginning with FDA approval could be created as a stand-alone option to replace other protections. Enhanced guidance and expedited review benefits currently available under the FDA's Fast Track, Breakthrough Therapy, and Priority Review programs (FDA, 2014) should also be extended to qualifying CNS drugs. Such a GAIN Plus Act for CNS drugs could be implemented tomorrow, converting the longer clinical development plus review time

disadvantage currently faced by the sector into a clear-cut advantage until such time that it is deemed unnecessary or replaced by more comprehensive policies. Boosting sector-specific market protection as a way to encourage industry to develop antiaddiction drugs was previously recommended by an IOM working group (Fulco et al., 1995).

Selectively Harnessing a Restricted Accelerated Approval Pathway

The combination of tier 1 and 2 changes outlined above, broad market protection reform recognizing innovation, plus an additional period of market protection accorded to breakthrough CNS drugs, will increase the attractiveness of neuroscience research to pharmaceutical companies, but their impact will be limited by the discounting routinely applied to future revenues in financial planning. Although extending the period of market protection might end up markedly increasing revenues for a commercially successful drug, the fact that the increase would occur about 25 years downstream of the launch of new drug discovery programs would add considerable uncertainty to projections and weaken impact on current industry decision making.

A more powerful pull incentive that could be put into place through a combination of policy initiative and regulatory agency action would be a modified harnessing of the FDA's existing Accelerated Approval track, created in 1992 largely to speed up public access to drugs for treating HIV/AIDS. This track allows drugs that fill unmet medical needs and target serious conditions to be approved quickly, based on affecting surrogate biomarker endpoints thought to be predictive of clinical benefits. Post marketing, sponsors are required to conduct studies to confirm drug efficacy using conventional clinical endpoints. In 1996 the Clinton administration instructed the FDA to apply the Accelerated Approval pathway more aggressively to cancer drugs, utilizing intermediate clinical endpoints such as tumor shrinkage in place of definitive endpoints such as patient survival (Clinton and Gore, 1996). By 2010, 35 cancer drugs had gained Accelerated Approval for 47 new indications (Johnson et al., 2011).

The Accelerated Approval track has so far had little impact on neuroscience drug development, but could be modified to have greater impact along lines recently discussed by the President's Council of Advisors on Science and Technology (PCAST, 2012). To improve overall progress in discovering and developing innovative new medicines, PCAST recommended that the FDA expand the use of its existing authority for Accelerated Approval to "all drugs meeting the statutory standard of addressing an unmet medical need for a serious or life threatening illness and demonstrating an effect on a clinical endpoint…or on a surrogate endpoint," noting also that the FDA should "actively engage the biomedical community in the development and evaluation of specific predictors" and "expand the scope of acceptable endpoints." The key challenge facing extension of the Accelerated Approval track to candidate CNS drugs is that the pathophysiology of major CNS disorders is less well delineated than the pathophysiology of HIV infections, where measurements of viral load and CD4 T cell counts provide powerful—albeit still imperfect—surrogate endpoints, or various cancers, where intermediate clinical endpoints often provide useful predictors of eventual clinical benefits. In addition, concerns have already arisen around the failure of several drugs marketed under Accelerated Approval to demonstrate efficacy in later confirmatory studies, as well as delays in accomplishing these required studies (Fox, 2005; Richey et al., 2009).

Thus, extension of Accelerated Approval to the neuroscience sector will need to be accomplished in the context of acknowledging that the uncertainties involved will exceed the historical standard for the track. This acknowledgment will likely take the form of a policy directive to the FDA, empowering the agency to accept these greater uncertainties (in the setting of reasonable safety information and appropriate ethical considerations) to make Accelerated Approval more available to neuroscience drug candidates—initially, to only a few best-case classes of drugs, highly selected for potential medical impact, strength of supporting science, and the availability of promising biomarker or intermediate clinical endpoints. A small program scale will facilitate active FDA involvement and surveillance, as well as the implementation of any midcourse adjustments that become indicated with experience. The Accelerated Approval granted under conditions of greater uncertainty might be furthermore specially restricted beyond precedents, stringently constraining, for example, advertising, drug label, pricing, and use, until additional safety and efficacy data can be collected. Restrictions might best be tailored to the circumstances of a given drug and treatment, recognizing that predictions of benefit/risk lie on evidence-based probability continua. An extreme restriction, appropriate for drug candidates with higher levels of associated risk, might even limit use to the context of large-scale clinical trials, if payors would agree to support partial reimbursement for such use (considering the savings they could accrue from successful drug development). For simplicity, there could be a single stage of Restricted Accelerated Approval prior to full approval, or restrictions could be progressively removed as additional data became available, an approach advocates have called "adaptive approval" (PCAST, 2012). CNS drug applications for Restricted Accelerated Approval should also benefit from other established preferred FDA handling mechanisms, including fast track and breakthrough therapy status, priority review, and fee waivers.

Such a staged approach to approval and marketing rights could help strike an optimum balance between patient risks and benefits, and also ensure that companies remained incentivized to pursue definitive clinical studies in a timely fashion. To avoid compromising ultimate financial returns, a full period of market protection should remain available after regular approval is granted (another reason to get away from dependence on patent clocks). Even implemented at limited scale, the availability of a Restricted Accelerated Approval pathway could constitute a significant pull incentive, bringing the point of revenue generation forward on the timeline so it could defray the costs of later definitive clinical trials, and providing a useful framework for gathering further clinical data. Each supported engagement could serve as an "anchor tenant" within industry research operations, providing capabilities that might be leveraged or shared by additional neuroscience programs. And one or two high-profile successes, demonstrating the tractability of key problems in CNS drug development, might go a long way toward restoring industry confidence in the sector.

An excellent initial therapeutic arena for application of a Restricted Accelerated Approval pathway might be disease-modifying drugs for Alzheimer's disease, already the proposed target of policy-based pull incentives (Lo et al., 2014; Davis, 2014); further, the FDA has already proposed use of a sensitive battery of cognitive tests in presymptomatic patients to demonstrate slowed progression (FDA, 2013; Kozauer and Katz, 2013). Perhaps Restricted Accelerated Approval could be extended to selected candidate drugs demonstrating promising effects on additional types of biomarkers, plausibly linked to pathophysiology and predictive of prevention or slowed progression, but not at the probability standard required by the existing Accelerated Approval pathway. The impact of the untreated disease is enormous, justifying the assumption of above-average risks in seeking treatments, and the gulf between effects in animal models and clinical efficacy has so far proved daunting. It may turn out that early clinical explorations will constitute the only practical way to identify effective treatments for a long time to come. A plethora of possible angles of attack (Franco and Cedazo-Minguez, 2014) and several promising biomarkers have been identified, although none of the latter have yet reached a level of strong validation (McGhee et al., 2014; Kozauer and Katz, 2013).

Other classes of candidate CNS drugs might also be considered for Restricted Accelerated Approval based on scientific attributes and projected risk/benefit: for example, drugs capable of ameliorating the core symptoms of autism spectrum disorders, improving cognition in schizophrenia, reducing brain tissue damage after ischemic insults, or overcoming various forms of addiction. The pathway would be well suited to supporting a provisional extrapolation from encouraging short-term studies to longer-term use, and might be brought to bear specifically to facilitate the development of combination (multiple active ingredient) therapies. The latter are difficult to bring forward through existing approval pathways, and may end up being necessary to treat a number of CNS diseases.

Tax Credits and Socially Responsible Investment Vehicles

Besides these main tiers of pull incentives, an additional potentially budget-neutral policy initiative might be aimed at securing current tax credits for CNS drug research. Since 1981, United States tax regulation has provided a refundable tax credit to companies engaged in drug R&D. However, the impact of this incentive has been limited by Congress's decision so far to perpetuate it through a series of extensions, rather than to make it permanent. The Government Accountability Office concluded in a 2009 study that the credit was effective in fostering innovation and economic growth, reducing industry costs of qualified research by 6.4%–7.3% (GAO-10-136). Yet, its temporary nature undermines its ability to be factored into decisions about drug discovery programs that may not be completed prior to its expiration. A policy initiative that guaranteed the credit specifically to support CNS drug R&D would not cost anything upfront—and perhaps ever, if the credits continued to be periodically renewed for programs across all therapeutic areas (as we would favor)—but would importantly encourage companies to keep bringing new CNS drugs forward.

Finally, it is worth mentioning one way to increase funding for drug research that would not have to compete for public funds: the creation of privately funded Socially Responsible Investment (SRI) vehicles focusing on various subsets of drug companies and selected foundation "venture philanthropy" engagements. Such vehicles could tap the massive pool of private wealth worldwide ($241 trillion in 2013 estimated by the Credit Suisse Research Institute), seeking individual investors willing to accept greater investment uncertainty in the context of promoting general or disease-specific advances against nervous system diseases.

Conclusion

To explore, modify, prioritize, and advance policy changes along lines outlined above, the larger neuroscience community—investigators, clinicians, and stakeholders—will have to convene, pool interdisciplinary expertise (including inputs from colleagues versed in law, government policy, economics, and ethics), debate vigorously, and finally speak with a clear and united voice spanning basic and clinical sciences, many professional guild lines, and a multiplicity of disease interests. This is not something we neuroscientists have excelled in doing historically, but the ongoing national BRAIN initiative is inspiring, and exemplars can be found in the effective policy advocacy of other groups, including those focusing on infectious diseases and cancers. The lead will need to be taken by our academic societies, patient advocacy groups, and nonprofit foundations, working closely with representatives from the White House, Congress, the FDA, and the NIH, as well as healthcare payors. The pharmaceutical industry cannot play a primary role, given conflict of interest, but should advise regarding the impact of various candidate policy changes on their decision-making processes.

Moreover, the pharmaceutical industry should be expected to contribute. Policy changes favorable to industry might be fairly linked to some key industry-side concessions, such as commitments to share and publish trial data, including negative data, and to ensure that new therapies are affordable and accessible. Any changes made to market protections, regulatory processes, or tax credits should be monitored carefully to ensure that the primary beneficiary is the public's health. Our free-market system has worked wonderfully to permit the discovery and development of many valuable medicines, but government regulation and periodic policy adjustments are expectedly necessary to optimize the public good—government's imperative. We emphasize that the initiative we describe here is not intended to produce a windfall for the pharmaceutical industry, but rather to benefit people with nervous system diseases, enabling companies to stay in the fight against these diseases while meeting their obligations to create sufficient value for their shareholders.

While discussion here focused on pull incentives, we also again underscore the essentiality of concurrent push incentives aimed at reducing the risks associated with pharmaceutical research. The former have the advantage of lower upfront costs, and may be for that reason an excellent place for the larger neuroscience community to hone its advocacy skills—the resultant organizational and policy momentum could only help advance the case for increasing public support for the entirety

of neuroscience research, including fundamental blue-sky research such as the BRAIN initiative.

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