



THE HUMANE SOCIETY
OF THE UNITED STATES

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Submitted to: cures@mail.house.gov

Comments on “21st Century Cures: A Call to Action”

To Rep. Fred Upton (R-MI) and Rep. Diane DeGette (D-CO):

On behalf of the Humane Society of the United States and our more than 11 million supporters who are concerned about the use of animals in research and the development of new cures, we thank you for the opportunity to provide comments and feedback on the questions raised in the white paper “21st Century Cures: A Call to Action.” We fully support the timely need to review the way the US approaches medical science.

There are currently 7000 known human diseases, but only 500 have treatments, which is partially due to the lack of clinical translation from animals to humans.^{1,2,3} The failure rate of drugs in clinical trials exceeds 90%, despite promising results from animal studies, and it requires an average of 13 years of testing and more than 1 billion dollars to see a drug become available to patients. Furthermore, according to a recent Bernstein report⁴, over the past 60 years, drug approval rates have declined rapidly despite the large increase in investment.

We agree with Representatives Upton and DeGette that there is an urgent need to re-think the way we conduct research in the United States if we want to help the patients and remain a world leader in research.

¹ Mak, I., Evaniew, N., Ghert, M., (2014). Lost in translation: animal models and clinical trials in cancer treatment. *Am. J. Transl. Res.* 6(2), 114-118.

² Perel, P., Roberts, I., Sena, E., Whible, P., Briscoe, C., et al. (2007) Comparison of treatment effects between animal experiments and clinical trials: systematic review. *B M J* 334: 197

³ US Food and Drug Administration (2004) Innovation and Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products. p. 8 Available at: <http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/ucm076689.htm>

⁴ The Long View: Pharma R&D Productivity – When the Cures Fail It Makes Sense to Check the Diagnosis, Bernstein Research, September 30th 2010

This includes the need to change the underlying paradigm of medical research and drug efficacy and safety analysis by moving away from empirical, animal-based experiments, and toward a system biology approach built on our vast knowledge of human biology and improvements in computer science and engineering, and re-evaluating current U.S. Food and Drug Administration (FDA) requirements.

Leveraging existing information

The proposal rightly describes capitalizing on all aspects of the drug development cycle, including drug research and development, clinical information, and post-clinical findings, and note that therapeutic development has not kept up with the “explosion in scientific knowledge.” To address both of these issues, Congress could facilitate, by funding and mandate, collection of all existing information into a common database in a way that facilitates use of this information in disease research and drug development, for example by populating a “knowledgebase” of biological of inter-related pathways and diseases analogous to the Adverse Outcome Pathway concept that is revolutionizing chemical safety testing.^{5,6,7} The US Environmental Protection Agency, the European Commission’s Joint Research Centre, and the Organization for Economic Cooperation and Development are working jointly on such a knowledgebase for toxicological applications.^{8,9} A similar approach for medical research and therapeutic evaluation is fundamental to maximally leveraging existing information to advance medical science. Such a knowledgebase works best when it builds on all communal information; therefore, public funding and access is recommended. US innovation could then focus on developing the tools necessary to best capitalize on this information to efficiently develop effective treatments. To accomplish this, Congress could initiate a visionary, interdisciplinary effort such as the “Human Systems Medicine Project” that would incorporate the elements described below.

⁵ Ankley, G., Bennett, R., Erickson, R., et al. (2010). Adverse outcome pathways: a conceptual framework to support ecotoxicology research and risk assessment. *Environ Toxicol Chem* 29, 730-741.

⁶ Kramer, V. J., Etterson, M. A., Hecker, M., Murphy, C. A., Roesijadi, G., Spade, D. J., Spromberg, J. A., Wang, M. and Ankley, G. T. (2011). Adverse outcome pathways and ecological risk assessment: Bridging to population-level effects. *Environmental Toxicology and Chemistry*, 30: 64–76. doi: 10.1002/etc.375.

⁷ Meek, M.E., Boobis, A., Cote, I., Dellarco, V., Fotakis, G., Munn, S., Seed, J., and Vickers, C. (2014). New developments in the evolution and application of the WHO/IPCS framework on mode of action/species concordance analysis. *J Appl Toxicol*. 34(1):1-18.

⁸ OECD. (2013). Guidance Document on Developing and Assessing Adverse Outcome Pathways. Series on Testing and Assessment, No. 184. Paris: Organization for Economic Co-operation and Development (OECD). <http://search.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono%282013%296&doclanguage=en> (accessed 21 May 2014).

⁹ Wittwehr, C. (2013). The Adverse Outcome Pathways Knowledge Base. Presentation to the OpenTox Euro 2013 meeting on 1 October 2013. <http://www.opentox.org/meet/opentoxeu2013/aop> (accessed 13 November 2013).

New, human-relevant, mechanism-based research and development tools:

As noted in the proposal, the great investment made in medical research has yielded some successes; however, there are several examples (the one given is Alzheimer's) of little progress despite significant outlay of effort and resources. This is due, in part at least, to the continued emphasis on animal models engineered in (usually failed) attempts to replicate the human disease. Investment in additional animal models, as well as continued investment in existing animal models, is unlikely to result in the kind of progress Congress is seeking to overhaul medical science. A recent publication by Langley¹⁰ highlighted the importance of utilizing existing, as well as developing and using new, tools in the field of Alzheimer's disease research. Several other publications, in the fields of asthma, sepsis, burn and trauma, have shown growing issues of reproducibility and relevance of the use of animal models^{11,12}

Investments in alternatives have led to the development of new technologies, such as the MIMIC system (Modular Immune *In vitro* Construct), which enables scientists at Sanofi Pasteur to test vaccines and drugs in an artificial human immune system. The National Institute of Health (NIH) and DARPA (Defense Advanced Research Projects Agency) awarded Harvard's Wyss Institute a grant to develop organs-on-chips to study complex human physiology outside the body. The Wyss Institute is working on integrating 10 different organs-on-chips to build an artificial human-on-chip, which will allow for drug development and safety testing. This project holds great promise, including for personalized medicine and development of cures for rare diseases.

We also encourage the continuity of the FDA's participation to discover, develop and approve new biomarkers which are important not only in diagnosis, prognosis, or for selecting appropriate patient therapy, but they can also help in understanding the mechanisms behind a disease and improve decision-making during drug development by delivering information about the mechanism of action of the drug, its efficacy, safety, and metabolic profile.

Development of these new methodologies should be a joint public-private venture, with Congress providing momentum through, for example, agency grants and matching funds.

We recommend to Congress to act rapidly by making sure that funding is allocated to the development of cures using human-biology-based models as well as the gathering of human information from research, including biomarkers and clinical trials, such as translational research that the National Center for Advancing Translational Sciences (NCATS) has been tasked to conduct.

¹⁰ Langley, G. (2014). Considering a new paradigm for Alzheimer's disease research. *Drug Discov Today*. In Press. Attached as annex.

¹¹ Seok, J., Warren, H.S., Cuenca, A.G., et al. (2013). Genomic responses in mouse models poorly mimic human inflammatory diseases. *PNAS*. 110(9):3507-3512.

¹² Buckland, G.L. (2011). Harnessing opportunities in non-animal asthma research for a 21st-century science. *Drug Discov Today*. 16(21-22):914-927.

The use of alternatives will be instrumental in developing treatments and cures faster and at a lower cost, making it affordable to a larger number of patients.

Collaboration

Last year, we sent our comments to NCATS addressing the issue of duplication, redundancy, and competition with industry activities. We believe that it is important to determine priorities and programs by establishing tight collaborations between the government (e.g. NIH, NCATS, FDA), research centers, patient advocacy groups, members and stakeholders of industry organizations including, but not limited to, the Pharmaceutical Research and Manufacturers of America (PhRMA), the Biotechnology Industry Organization (BIO), and the National Venture Capital Association (NVCA), but also with animal advocacy groups focusing on striving changes for better science. In order to be efficient in the discovery of new drugs, there is an undeniable need to collaborate and share data generated from fundamental and pre-clinical research, but also from clinical trials, and the role of regulators under the FDA is vital in this collaboration.

We suggest that funding be attributed to priority projects and grant proposals be made available to address those priorities in a fashion coordinated with the various stakeholders.

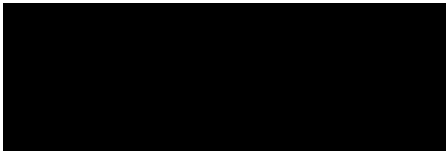
FDA involvement

Current preclinical drug investigations rely heavily on empirical animal studies that were developed decades ago from which little mechanistic information can be obtained. Based on the authorizing law and regulations, however, FDA has flexibility to determine specific preclinical requirements and methods of data acquisition, and requirements and the ability to discuss preclinical investigations with the submitting industry. FDA could improve preclinical drug investigations by maximizing this flexibility to include mechanistic information from the types of human-based methods and information described above. FDA could go further in requiring the use of non-animal data whenever possible and considering data generated using methods that have been developed by the industry but not yet formally accepted for regulatory purposes. To maximize FDA's ability to do this, regulators need to be kept informed on the latest scientific developments, and there needs to be good communication between, and amongst, those responsible for reviewing submissions. Flexibility, education, consistency, and transparency should be the pillars of the FDA review process.

We highly encourage Congress to consider these comments as we believe they would allow for faster, more efficient drug discovery and development process and more effective cures. This

would help millions of patients in the United States and beyond and keep our country a leader in advanced biomedical research throughout the world.

Sincerely,



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Senior Director of Policy and Advocacy



ANNEX



Considering a new paradigm for Alzheimer's disease research

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Using Alzheimer's disease as a case study, this review argues that it might be time to consider a new paradigm in medical research and drug discovery. The existing framework is overly dependent on often unvalidated animal models, particularly transgenic mice. Translational success remains elusive and costly late-stage drug failure is common. The conventional paradigm tends to overlook species differences and assumes that animal-based findings are generally applicable to humans. Could pathways-based research using advanced human-specific models probed with new tools, including those of systems biology, take centre stage? The current transition in chemical toxicology to a 21st-century paradigm could be a model for health research, with probable medical and economic benefits.

Introduction

Total new drug approvals have continued to fall whereas the costs of producing novel medicines have grown exponentially. Despite increasing investment, 92% of all novel drugs fail in clinical trials, mainly because of unpredicted toxicity or insufficient efficacy in humans [1]. Problems in basic medical research, drug discovery and effective translation from laboratory to clinic are widely recognised. Meanwhile, in chemical toxicology a transformation is already unfolding, following a seminal report from the US National Research Council in 2007 [2]. This recommended a '21st-century paradigm' for safety testing, involving an explicit transition away from a reliance on adverse endpoints in animal tests and towards a novel framework based on understanding toxic perturbations to cellular pathways, mainly using *in silico* tools and human-specific cell and tissue models. The National Research Council's vision is being implemented actively worldwide, including by the US multi-agency Tox21 consortium [3] and the Environmental Protection Agency's multi-million dollar ToxCast programme [4].

A recent refinement in toxicology is the concept of adverse outcome pathways (AOPs), which are intended to provide clear mechanistic representations of critical toxic effects spanning molecular, cellular, organ, individual and population levels. AOPs have a common structure comprising exposure to the first molecular

initiating event (e.g. a chemical binds to a cell receptor), intermediate steps and key events and an adverse outcome that (in toxicology) could for example be cancer, allergy or liver damage. The first validated AOP (for skin sensitisation) has now been accepted at the Organisation for Economic Cooperation and Development and several further AOPs are in draft form [5].

The transition in toxicology could provide a template for modernising the disease modelling and drug discovery paradigm. Developments in systems biology have enabled studies of human gene pathways and networks linked to disease, and expanding this concept to an AOP approach would have obvious relevance, widening consideration of disease pathways to include environmental factors at the start of the pathway and whole-person or population-level outcomes at the pathway's conclusion. Incorporating advanced scientific tools into a research framework emphasising pathways and networks in human-specific models could offer better progress towards understanding and treating diseases than the current emphasis on animal models.

The animal model paradigm

For many decades, animal models have had key scientific and conceptual roles in health research and drug discovery, because human experimentation was unethical and impractical and *in vitro* models were simplistic and poorly representative of the *in vivo* situation. Within the traditional research paradigm, animal models remain dominant and animal data are used in a 'gate-keeper'

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role [6] for studying pathophysiological mechanisms, for probing novel therapeutic approaches and as preclinical models in scientific guidelines [e.g. those of the International Conference on Harmonisation (<http://www.ich.org>)].

The animal model paradigm, although widely supported [7], has also been described as ‘seriously flawed’ and ‘not well suited’ for predicting human responses in clinical trials, where failure rates are very high [8]. Some authors refer to a ‘crisis of validation’ for animal models in neuroscience drug discovery, leading to a high risk of developing mainly ‘me-too’ compounds [9]. Van Meer and colleagues describe the current approach as ‘a stalemate in which animal studies, predictive or not, continue to exist with little room for innovation’ [10]. They and others call for a critical assessment of the predictive value of animal studies, from which it might emerge that new technologies can be implemented that predict efficacy as well as, or better than, animal studies.

The regulatory requirement for preclinical animal data has been challenged, because much is of ‘unclear relevance’ to human disease [11]. Tacit assumptions about the adequacy of rodent models in disease research need to be questioned [12]; it is too often simply assumed that there are good correlations between an accepted animal model and human subjects [13]. An analysis of 76 highly cited studies on a range of animal species published in seven high-impact scientific journals found that only 37% accurately predicted human outcomes [14].

Despite sustained investment in animal models, disease-modifying therapies remain elusive for major illnesses such as Alzheimer’s disease (AD) [15], stroke [16], motor neuron disease [17], Huntington’s disease [18], asthma [19], sepsis [20] and inflammatory diseases [6]. The animal-model paradigm tends to discourage a critical appraisal of the differences between species and encourages a view that animal-based findings are generally applicable to humans [21]. However, evolutionary biology dictates that the species barrier cannot be overcome and significant differences between animal models and human diseases will continue to frustrate progress. For example, it is hard to envisage how animal models, limited by inter- as well as intra-species variations, could expedite the development of more personalised medicine.

Animal studies can provide useful *in vivo* data about selected pathologies, such as the amyloid pathway in AD research, but increasingly this research could be conducted using novel human- and disease-specific models and tools. These models and techniques are being incorporated into research in a piecemeal manner but without a serious review of the long-standing gate-keeper role of animal studies. It was the recognition that animal tests were inadequate and that advanced research tools were being insufficiently exploited in chemical toxicology that led to the transition currently progressing in that field [2].

With developments in systems biology, a systems understanding of human disease pathophysiology is moving within our reach [1]. The coming together of a crisis of confidence in animal research with the emergence of much better human *in vitro* models [22] and advanced techniques for human *in vivo* studies creates a timely opportunity to review how a new paradigm could best incorporate these advances in a coherent research framework. AD research is examined here as a case study of the limitations of the present research framework, how a new vision for medical research might look and the potential benefits it could achieve.

BOX 1

Classic pathologies of Alzheimer’s disease (AD)

Underlying the progressive cognitive deficits of AD are three classic pathologies: extracellular plaques containing amyloid peptides; intracellular neurofibrillary tangles (NFTs); and neuronal degeneration including synaptic loss.

Amyloid plaques occur mainly in the cerebral cortex and in the hippocampus, regions of the brain associated with higher cognition and memory function. The plaque cores are formed from abnormally folded amyloid- β ($A\beta$) peptides, generated from the proteolytic actions of β - and γ -secretases on the larger amyloid precursor protein (APP). Presenilins form part of the γ -secretase complex which, together with β -secretase, cleaves APP.

According to the amyloid cascade hypothesis, APP processing is abnormally shifted towards $A\beta$ production. This leads to increased amounts of $A\beta_{39-42}$ aggregating into insoluble plaque-forming fibrils that disrupt neural function. Amyloid plaques often appear many years before people develop symptoms of AD and amyloid burden alone poorly predicts cognitive function.

Intracellular NFTs comprise hyperphosphorylated and abnormally aggregated forms of tau protein. Normal tau promotes the assembly and stability of neuronal microtubules but when hyperphosphorylated it aggregates into NFTs in neurons, leading to cell death. The deposition of tau aggregates correlates spatially and temporally with the development of dementia in AD. However, despite the obvious significance of tau in AD, no tau mutations have yet been associated with the human disease.

Synaptic and neuronal degeneration comprise the third characteristic pathology of AD. Changes in synaptic density correlate strongly with decline in cognitive ability. The neurons of the hippocampus and the association areas involved in all other cognitive functions become increasingly dysfunctional, with loss of dendritic spines and synapses. Neurotransmitter pathways start to fail, notably but not only the cholinergic system. Progressive brain atrophy, particularly in the neocortex and hippocampus, is observable in structural magnetic resonance imaging (MRI) scans.

Alzheimer’s disease: translational failures

AD is a progressive dementia (Box 1) with classic pathologies comprising amyloid plaques in the brain, neurofibrillary tangles (NFTs) containing abnormal tau and neuronal degeneration. Symptoms include cognitive deficits, including memory disruption and impaired judgment, disorientation, confusion, behavioural changes and difficulties moving, speaking and swallowing. Ultimately fatal, AD causes suffering to patients and their families over a long period of time. The prevalence of AD worldwide is expected to triple over the next 40 years, so the need for progress is very pressing.

The five approved drugs for AD can stabilise symptoms temporarily, but do not slow disease progression. Around half of patients benefit modestly [23], but there is an urgent need for better, disease-modifying therapies as well as preventative measures. The link between cholinergic deficits and AD, first discovered through analysis of post-mortem human brain tissue in the 1970s and 1980s and then pursued with animal studies, led to the four existing cholinesterase inhibitor drugs. Since the approval of memantine (a glutamate receptor blocker) a decade ago, many novel compounds for AD have entered clinical trials, but so far none has successfully completed a Phase III trial despite encouraging preclinical results in transgenic (Tg) mice (Table 1).

TABLE 1

Results from Tg mouse studies compared with recent Alzheimer's disease (AD) clinical trial outcomes

Generic drug name (trademark name) and company	Proposed mechanism of action	Preclinical Tg mouse results	Clinical trial results	Refs
AN1792 Elan	A β 1–42 peptide, active immunotherapy targeting amyloid pathway.	Generated anti-A β antibodies that reduced plaques, neuritic dystrophy and astrogliosis in older PDAPP mice and prevented these pathologies in younger animals. No meningoencephalitis.	Phase II, terminated 2002: removed plaque but failed to affect cognitive decline. No improved survival or time to severe dementia. Several patients developed autoimmune meningoencephalitis.	[78,79]
Tramiprosate (Alzhemed™), Neurochem	An amino acid that binds to A β monomers to prevent plaque formation.	In TgCRND8 mice reduced brain amyloid plaque by 30% and reduced plasma A β levels.	Phase III: no cognitive improvement, no significant treatment effect seen. Withdrawn from development.	[80,81]
Tarenflurbil (Flurizan™), Myriad	Gamma-secretase modulator intended to reduce A β .	Attenuated spatial learning deficits if given early in Tg2576 mice. Older Tg2576 mice had significant decrease in plaques.	Phase III: did not slow cognitive decline or delay loss of normal daily activities. Discontinued for AD indications.	[82,83]
Semagacestat, Eli Lilly	Gamma-secretase inhibitor, intended to reduce production of A β plaques.	Reduced plaques and lowered A β in plasma, CSF and brain in a dose-dependent manner in PDAPP Tg mice.	Long-term Phase III: failure to slow disease progression and did not improve cognitive status. Patients on higher dose had significant worsening of functional ability. Trial stopped 2010.	[84,85]
Tideglusib, Noscira	Inhibitor of glycogen synthase kinase-3, intended to reduce tau hyperphosphorylation.	In Tg mouse models, it reduced lesions including A β and tau deposits, gliosis and neuronal loss, and significantly improved behavioural impairments.	Phase II, 2012: company announced that primary cognitive endpoint and two of the secondary endpoints were not met (http://zeltia.com/actualidad.cfm?anyo=2012&semestre=2)	[86]
Rosiglitazone (Avandia®), GlaxoSmithKline	Antidiabetic drug that activates peroxisome proliferator-activated receptors.	Reduced A β 1–42 levels without affecting amyloid deposition, and improved spatial learning and memory function in Tg2576 mice.	Phase II: modest cognitive improvement in non-APOE* <i>e4</i> subjects but decline in APOE* <i>e4</i> patients. Phase III: no significant cognitive efficacy at any dose, in any test group. Trials discontinued.	[87,88] [89]
Atorvastatin (Lipitor®), Pfizer	Statin targeting amyloid pathway.	Markedly attenuated brain A β deposition in PSAPP doubly Tg mice.	Large-scale randomised controlled trial for mild-to-moderate AD: no benefit to cognition or global function compared with placebo.	[90,91]
Bapineuzumab, Pfizer and Janssen AI	Humanised monoclonal antibody: passive immunotherapy intended to bind and clear A β .	An anti-A β monoclonal antibody (3D6) substantially prevented and/or reduced amyloid deposits in cerebral vasculature in PDAPP mice.	Phase II: weak to nonexistent clinical benefits on cognition. High doses caused brain oedema and microbleeding in some patients. Phase II: decreases in total tau and phosphorylated tau in CSF. No clear changes in CSF A β . Two Phase III trials, 2012: no clinical benefit in mild-to-moderate AD compared to placebo. Development scaled back.	[92,93] [94] [95]
Solanezumab, Eli Lilly	Humanised monoclonal antibody: passive immunotherapy intended to bind and clear soluble A β .	Acute and subchronic treatment of Tg mice attenuated or reversed memory deficits.	Two Phase III trials, 2012: dose-dependent increase in unbound cerebrospinal fluid A β 1–42, but no change in cognitive decline or functional ability in mild and moderate AD. Secondary analysis suggested it slowed cognitive decline in patients with mild AD (http://www.hcplive.com/conferences/aan-2013/Efficacy-and-Safety-of-Intravenously-Administered-Solanezumab-in-the-Treatment-of-Patients-with-Mild-to-Moderate-Alzheimers-Disease)	[96–98]
Latrepidine (Dimebon), Pfizer and Medivation	Oral antihistamine with proposed but unproven effect on mitochondria.	Treated TgCRND8 mice showed improved learning behaviour and less accumulation of A β 1–42 and α -synuclein (conducted after clinical trial).	Phase II results, Russian trial 2008: improvements in cognitive, global, daily function and behaviour endpoints. Phase III, 2012: patients with mild-to-moderate AD showed no improvement in cognition or functional ability.	[99,100] [101]

Abbreviations: A β , amyloid- β ; CSF, cerebrospinal fluid; PDAPP mice, (Tg) transgenic mice overexpressing mutant human amyloid precursor protein V717F.

BOX 2

Common reasons for failures of translational research

- Methodological flaws and poor design in preclinical studies, leading first to systematic bias and then to inadequate data and incorrect views of efficacy.
- Critical disparities between humans and animals (and also within animal species), including pathophysiological differences, which result in unreliable outcomes.
- Disparities between animal studies and clinical trials (e.g. in comorbidities, the use of co-medication, the stage of disease, the timing and dosing of the test treatment, and selection of outcome measures).
- Insufficient reporting of details of animals, materials and methods.
- Publication bias, which could account for a substantial part of the efficacy reported in the experimental literature for various diseases.

There are many acknowledged reasons for failures of translational research (listed in **Box 2**) [24]. Although numerous improvements can be made to the methodology of animal studies, including for AD [15], they remain inevitably flawed by: the 'insuperable species barrier' [13], comprising fundamental underlying species differences between animals and humans; the disparities between animal models and human diseases in complexity, causation, pathophysiology and progression; the uncertain relevance to humans of the results of behavioural studies in animals [25].

The limitations of mouse models in AD research

Some AD research is conducted in dogs, primates, ageing rats and chemical- and lesion-induced rodents, and newer models include genetically modified zebrafish and the nematode worm *Caenorhabditis elegans*. However, by far the dominant animal models over the past 15 years have been Tg mice. Most of the Tg mouse lines are based on one or several inserted human genes relevant to the amyloid hypothesis of AD causation [7,26].

The reliability of a model is considered in terms of its validity (summarised in **Box 3**) [27]. Regarding face validity, some lines of Tg mice develop plaques and/or NFTs, a few show some neuronal loss and some have cognitive deficits. However, the disease

BOX 3

Considering the validity of a human disease model

An established framework posits three types of validators: face, construct and predictive validity.

Face validity addresses phenomenological similarities between a model and a human disease. Although useful in the development of a new model, face validity is less suitable for validating a model, because superficial similarities do not always have the same underlying mechanisms or pathways.

Construct validity addresses the theoretical rationale, asking whether the model reflects the etiology and underlying mechanisms or pathways of the human disease, and if the outcome measures match the clinical setting.

Predictive validity asks whether a model accurately predicts what happens in humans, especially the effects of therapeutic interventions. It is a key factor in translational science.

dynamics differ, none of the models fully recapitulates AD and the phenotypic similarities are species- and strain-dependent. In the case of construct validity, although sporadic AD (sAD) is dominant in humans, Tg mouse genotypes resemble the much rarer (~5% of cases in humans) familial AD (fAD). In humans, fAD is linked to mutations in the amyloid precursor protein (APP), presenilin 1 and presenilin 2 genes, none of which singly or combined leads to a full spectrum of AD pathologies in mice. None of the Tg mouse lines overexpressing APP 'by any stretch of the imagination' develops cognitive or behavioural deficits approaching those typical of AD [7]. Some Tg mice expressing human tau variants have a fuller pathology, but in humans these tau variants are not associated with any form of AD. Triply Tg mice, generated using presenilin 1 knockin mice and micro-injecting APP and FTDP-17 (a tau mutation) transgenes, develop amyloid plaques, NFT-type lesions and deficits in spatial memory; but they reflect a composite of two distinct diseases neither of which is AD.

Few AD cell pathways are known and those studied in Tg mice, such as amyloid deposition, are considered to have generated useful mechanistic data but are limiting in terms of novel drug targets and have been poorly predictive of clinical outcomes. The development of Tg mice for model human disease pathways can only be attempted once a pathway is known to be significant in patients. Emerging human- and disease-specific models potentially offer a way out of this stalemate by enabling the discovery and detailed study of new human pathways and drug targets.

In translational science predictive validity is crucial. Studies of Tg mice have certainly contributed to an understanding of some AD pathways and more than 300 interventions have been tested as a result; however, as discussed above, none has translated into disease-modifying therapies [7,15]. Models that meet more levels of validity are clearly of higher utility and relevance than those where validity is weaker. Most animal models, including those for AD, do not fulfil sufficient validity measures and the conclusions that can be drawn from their use should be more strongly qualified [13].

Many animal models have never been evaluated systematically, for example by systematic review and meta-analysis of performance characteristics such as reproducibility, specificity, sensitivity, clinical relevance or mechanistic basis [28]. At the time of writing, no systematic reviews have been published about the predictive ability of Tg mouse models of AD. This is in stark contrast to recommendations that systematic reviews of the clinical relevance and the risk of bias of preclinical research should be conducted before the start of clinical trials [29,30]. Without systematic evidence of validity, the utility of animal models including Tg mice in AD research is unproven; and yet costly clinical trials, of potential risk to participants, are conducted primarily on the basis of these data.

The species barrier is a highly significant problem in developing valid models of human diseases. Mouse models seldom sufficiently recapitulate human disease pathways and pathologies, including in AD, because of important underlying species differences in genetics, protein pathways, metabolism, pharmacology and physiology that have accumulated since rodents and humans diverged 65–85 million years ago. Evolutionary divergence in protein functions and gene regulatory networks can complicate studies in animals, and it should not be assumed that gene function is

conserved between animals and humans until functional equivalence is demonstrated [31]. In considering AD, unlike humans mice are naturally resistant to age-related amyloid pathology. Mouse and human APPs differ by 17 amino acids – three in the amyloid- β peptide ($A\beta$) sequence. Knockin mice with *APP* mutations express humanised $A\beta$ but do not develop amyloid plaques or neuropathology [26], implicating fundamental differences such as a shorter lifespan or dissimilar processing of mouse APP by β -secretase. Mouse brain only has 4R tau, whereas human brain has 3R and 4R tau isoforms that are both hyperphosphorylated in AD. There are 14 amino acid differences in the N-terminal region of human and murine tau, and the difficulties in inducing NFTs in mice could be attributable to these disparities [26].

Only humans have genetic variants of the apolipoprotein E gene (*APOE*), a major gene associated with sAD. Human *APOE**e4 has a unique domain interaction between the Arg61 and Glu255 residues, responsible for most of its associated neuropathology. The one murine *APOE* has Thr61 instead of Arg61, preventing the *APOE**e4 domain interaction. Researching the role of *APOE**e4 in mice has necessitated the generation of complex Tg lines, possibly introducing confounding issues. Presenilin 1 correlates highly with oligodendrocyte markers only in humans, not in mice [32]. The human presenilin 2 promoters are modulated differently from the murine equivalent, and presenilin mutations produce almost no plaque pathology in Tg mice.

A major known risk factor of sAD is ageing. Humans experience a dramatic increase in age-dependent repression of broad-spectrum neuronal genes compared with mice, likely to alter neural networks and result in cognitive changes. Adult neurogenesis occurs significantly in the rodent hippocampus but is much less obvious (or absent) in longer-lived species, including humans [33]. Of 49 well-known genes examined in the mouse cortex and hippocampus, over 50% showed inter-strain expression variation, with probable consequences for behaviour and drug responses [34]. Neuronal nitric oxide synthase is prominently expressed in C57B6 mice but its levels are much lower in SV129 mice. Fundamental strain- and species-dependent variations such as these cause difficulties in extrapolation from rodent data to humans. In different species, functionally equivalent receptors can have distinctive pharmacological profiles. Currently, drug candidates are frequently optimised for rodent pharmacology and the first time a novel drug is challenged by a range of human pharmacologies is often at the clinical trial stage, when failure is very costly.

In Tg mice, connections between the increase in $A\beta$, lesions and symptoms have resisted clarification. Many mice show behavioural changes before significant plaque deposition – the reverse of the human situation. The relative abundance of $A\beta$ peptides in APP23 mice and AD patients differs, suggesting dissimilar mechanisms underlying amyloid deposition. In AD brains the unfolded protein response is upregulated; but in Tg2576 mice neither the unfolded protein response nor the cell-death pathway is induced [35]. There are also species variations in post-translational modifications of amyloid peptides and their resistance to degradation, thought to be related to differences in lifespan and physiology between mice and humans.

One of the strengths of *in vivo* models of AD, and a contributing feature of their construct and predictive validities, should be the opportunity to measure relevant behavioural indicators of

cognitive deficits. Tg mouse models are sometimes defended as essential because learning and memory deficits are core to AD and cannot be replicated in conventional *in vitro* models. But functional studies with Tg mice are not predictive and it is not known how, if at all, behavioural tests reflect AD cognitive deficits [26]. Philipson *et al.* point out that behavioural studies with Tg mice can be relevant to understanding whether an amyloid species or a pathology has a functional effect on neurotransmission but are inadequate for predicting whether a drug alters AD symptoms [36].

Functional studies in mice are also poorly reproducible, between and even within laboratories, and test performance is influenced by the selected promoter gene, by transgene overexpression and by the choice of background strain [37]. Some strains are notably aggressive, neophobic or anxious which confounds interpretation of aspects of cognitive performance, and some perform particularly badly in the Morris water maze test of spatial memory [38]. In the mid-1990s, Tg2576 mice were reported to have a memory deficit that correlated with amyloid plaques, but this was challenged [39] and the argument was still rumbling on nine years later. Dramatically different phenotypes can arise from using the same mutations and promoters, and Tg mouse lines are subject to sensorimotor and cognitive impairments that do not replicate AD [40]. Cognitive deficiencies in Tg mice are not only age-dependent but also task- and sometimes gender-dependent, making extrapolation to humans very difficult.

Under the current research paradigm, the mainstream opinion is that animal models remain necessary and should be improved [9,13,15,36]. For example, it has been argued that disease endpoints other than massive $A\beta$ deposits could be used in rodents and might have more translational relevance. Olfactory dysfunction, an early symptom in AD, could provide a marker of disease progression and drug effect in Tg mice [41]. Such developments could yield improved predictive validity over existing Tg mouse models, but further research and validation will take time and the poor face and construct validities of mouse models, as well as the species barrier, would remain unaddressed. With the emergence of 21st-century human-specific models and tools, positioning human rather than animal pathophysiology at the centre of research efforts might be more productive [6].

Advances in human cell models and tools

Until recently, research and drug discovery in AD (as in other fields) have been hampered not only by animal models of limited utility and unproven validity but also by overly simplistic human cellular models. The standard cell models have often used cancer cell lines with many genetic changes in static, monolayer culture, which fails to replicate the architecture, cellular interactions, differentiation status and functionality of human tissue [42].

But this century has seen new advances in human cell models and applicable tools, which are expected substantially to increase the value and relevance of human cell-based research. Human induced pluripotent stem cells (hiPSC), generated by reprogramming adult human cells and differentiated *in vitro*, provide significant opportunities for generating unique disease-relevant, tissue- and human-specific cell models, even in genetically complex diseases such as sAD. hiPSC generated from patients with fAD and sAD have been differentiated into functional and electrophysiologically active neurons [43] with increased $A\beta$ 1–40, active

glycogen synthase kinase-3b and phosphorylated tau. In another study, A β peptides accumulated in neurons and astrocytes derived from hiPSC from fAD and sAD patients, leading to endoplasmic reticulum and oxidative stress. The research further demonstrated the usefulness of patient-specific hiPSC in probing AD pathogenesis and evaluating drugs [44]. Thus, hiPSC studies are expected to provide novel insights into pathways of AD initiation and pathogenesis, the roles of different cell types, drug screening and development studies, patient-specific drug responses, prospective diagnostics [45] and the role of sAD susceptibility genes identified in genome-wide association studies (GWAS). hiPSC derived from individuals with genetic variations of interest and differentiated into neural cells can now be deep-sequenced using high-throughput, automated technology. The combined availability of patient- and disease-specific genetic material and living *in vitro* models could help achieve the ultimate goal of relating genotype and phenotype, for example correlating individual genetic variants with gene expression patterns, cellular disease pathways and altered functions of neural cells [46].

Another adult human source of pluripotent stem cells is the olfactory mucosa, which is easily biopsied or sampled post-mortem. Post-mortem olfactory stem cells from individuals with Alzheimer's disease showed differences in APP processing and oxidative stress, and *in vitro* models of neurological diseases based on biopsied human olfactory stem cells offer several practical advantages over hiPSC for drug discovery [47].

So that human stem-cell-derived models can achieve their full research potential, optimisation of reprogramming techniques for somatic cells, identifying markers that predict differentiation potential, improving *in vitro* differentiation protocols and generating purer cell populations are some of the challenges that must be overcome [42]. Where post-mortem tissue from the same patient is available, detailed findings in hiPSC-derived cells *in vitro* can be directly validated. Acknowledging that animal disease models are time-consuming, costly and predict drug efficacy in humans imperfectly, the US National Institutes of Health (NIH) envisages that better target validation using human tissues and hiPSC could eliminate testing for drug efficacy in animals altogether [48]. Grskovic and colleagues also foresee hiPSC technology providing a new, human-disease-based drug discovery paradigm, in which older models (including 'nonpredictive animal models' and simplistic cell cultures) are replaced, leading to human efficacy and toxicity data being available earlier and even moving directly 'from *in vitro* clinical trials to actual clinical trials' [49].

In vitro clinical trials would provide human efficacy (and toxicity) information at multiple dose levels and data on the heterogeneity of the patient population, minimising risks of later failures and achieving faster timeframes with lower-cost, high-throughput biological platforms [49]. A clearer understanding of genotype-phenotype relationships in disease-specific human cells is also on the horizon, potentially providing a crucial link between basic research and translation. Patient-derived hiPSC models should be able to identify hits that alter the disease phenotype, as well as having promise for target validation, lead optimisation, candidate selection, biomarker discovery and personalised medicine [50].

Tissue engineering creates robust and controllable 3D *in vitro* human tissue models that better replicate the *in vivo* spatial environment. Compared with 2D cultures, tissue engineered

models have improved viability and many cellular and tissue processes are closer to the *in vivo* situation. The production and function of these tissue constructs can be tightly controlled with fewer confounding factors than when using living animals, and they are expected to have promising applications in disease modelling and toxicology [51].

Microfluidics technology employs microchip devices incorporating a laminar flow of culture medium, improving the transport of nutrients and waste products. They offer rapid, reproducible and sensitive platforms compatible with high-throughput processing or high-content analysis. Organ-on-a-chip devices combine microfluidics with 3D culture, aiming to reproduce key structural, functional and biochemical features of human organs *in vitro*. Human lung and gut are two of several models available, with brain-on-a-chip systems currently under development [22]. These technologies are another key tool to create high-quality, high-throughput *in vitro* models for better testing of drug efficacy and toxicity, and potentially for studying disease pathways and identifying new drug targets in human-relevant systems [22,52]. The NIH anticipates that they have 'the potential to change paradigms of how we develop therapies, inform regulatory decision-making process and shorten clinical trials' (<http://www.ncats.nih.gov/about/faq/tissue-chip/tissue-chip.html>). There have also been developments in electrophysiological techniques applicable to human cells *in vitro*, providing key functional data. Automated patch-clamping combined with microfluidic channels now yields sensitive, high-quality, high-throughput data including measurements of very fast ligand-gated ion channels and receptors in cell lines [53].

In AD research, studies of deficits in learning and memory have classically relied on mouse models [9] and *in vitro* alternatives are not yet validated. However, if human neural networks can be studied reliably *in vitro*, they could overcome a key challenge: assessing drug effects on aspects of learning and memory. A reliable tool for functional studies would improve translational success, because rodent models are poorly reproducible [37], time-consuming [36] and of unknown relevance [25]. Microelectrode array devices populated *in vitro* with human-stem-cell-derived neuronal cells allowed functional studies of spontaneous network activity and neuronal receptor responses over several weeks and studies of mechanisms underlying learning and memory [54]. Optogenetic techniques combined with multielectrode arrays applied to cultured neuronal networks enable studies of short-term memory mechanisms *in vitro*, and should provide a rapid screening tool for drugs [55]. Human cortical development to the level of functional synapses and networks has recently been achieved *in vitro* using hiPSC, opening the door to novel functional models resembling the *in vivo* cortex in circuit specificity and laminar organisation of cortical projection neurons [56]. These emerging human models certainly need further investment.

The wide range of emerging human-specific cellular models and 'next-generation' tools with which to probe them are undergoing rapid development and validation. If their potential is realised they will become game-changers for disease research and drug discovery.

Human tissue and omics analyses

Human post-mortem tissue research into AD has declined since it led to the discovery of the cholinesterase-inhibitor drugs, but that

will change as better quality specimens become available and next-generation sequencing enables a rapid and unbiased characterisation of messenger RNA, proteins and metabolites associated with disease. New transcriptomics analyses needing no *a priori* etiological hypotheses will advance understanding of AD pathogenesis. In 2013, an elegant study integrated publicly available data from GWAS with that from human cortical transcriptional networks and human neuroimaging, to advance knowledge of key regulatory molecules and pathways involved in APOE-related risk of AD [57]. Laser-capture microdissection enables gene expression profiling of selected cortical neurons from post-mortem brain, and has revealed significant differential expression of AD-implicated genes in regions of AD brains compared with controls. In the epigenetics field, research is underway to elucidate specific genes affected by epigenetic changes and whether these implicate proteins and pathological processes relevant to AD [58].

Human pathology can also be probed by analysing cerebrospinal fluid (CSF) or blood samples from subjects at different disease stages, and linked with neuroimaging and magnetic resonance spectroscopy data. Current diagnostic guidelines for AD include three CSF biomarkers [59] and these human *in vivo* data are of potentially high value to understanding AD pathology, following disease progression and developing new drugs [59].

Quantitative proteomics offers comprehensive insights into disease phenotypes and pathways and advanced analytical techniques have dramatically improved in speed and precision. An analysis of cortical samples of AD and normal brains using high-resolution mass spectrometry [60] recently identified and quantified 197 proteins of significantly different abundance in AD brain samples. Mapping with bioinformatics tools revealed associations with multiple pathways and processes important in AD. Protein identification with capillary electrophoresis coupled to an electrospray ionisation time-of-flight mass spectrometer was used recently with AD brain tissue to reveal abnormal phosphorylation in nine proteins that influence cell metabolism, signal transduction, cytoskeleton integration and synaptic function [61].

Advanced human *in vivo* studies

Neuroimaging is one expanding approach to human *in vivo* research in AD and other neurological disorders. Imaging technologies are advancing rapidly in specificity and sensitivity, in spatial and temporal resolution, and in automated image analysis, impacting progress in elucidating pathways of human disease, early diagnosis, patient stratification, personalised therapies and treatment evaluation, including effects on cognitive dysfunction. Safe human *in vivo* studies are a key component of a new research paradigm, also providing a species-relevant link that helps inform and validate *in vitro* techniques.

Ultra-high-field magnetic resonance imaging (MRI) can now directly visualise cortical plaque disposition and early tissue loss in the hippocampus of patients previously only visible in post-mortem tissue [62]. Multimodal magnetic resonance tools can measure and correlate structural, functional, metabolic and haemodynamic changes in the brain and have been used in several studies of AD. Magnetic resonance spectroscopy detects and quantifies *in vivo* metabolites that reflect the status of neuronal and glial

cells, energy metabolism, inflammation and neurotransmitters. Improvements in sensitivity are expected to lead to progress in real-time monitoring of *in vivo* metabolic processes in the human brain. Diffusion tensor imaging traces neural tracts and microstructural damage in white matter in the human brain that can be correlated with omics, pathogenesis, disease progression and cognitive features of AD.

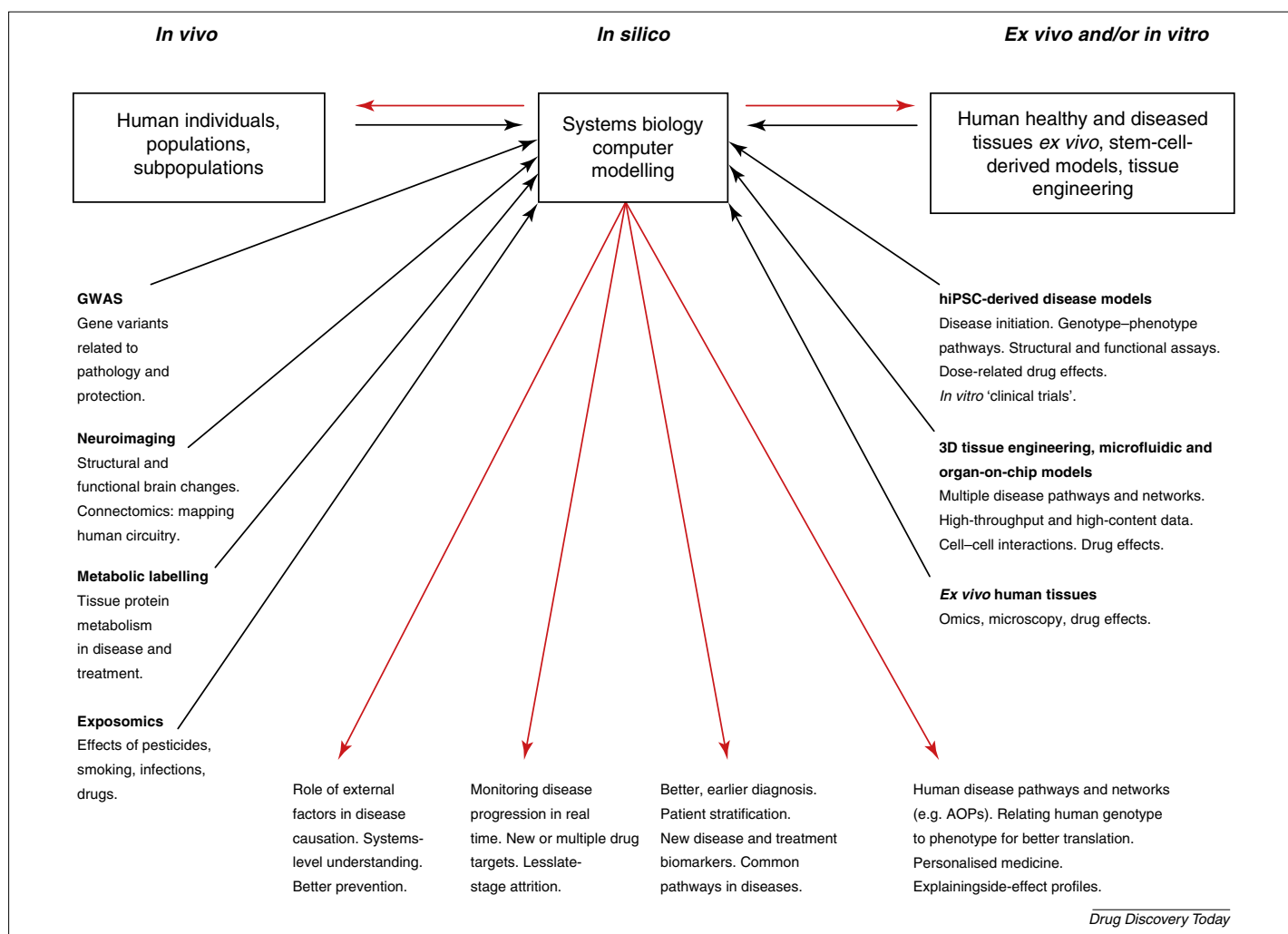
Positron emission tomography (PET) studies in patients have revealed new information about plaque distribution and some clinical trials have exploited A β as a biomarker. In 2013, a new tau ligand was developed that enables sensitive PET imaging of tau NFTs in living patients with AD for the first time [63]. This development offers exciting possibilities for earlier AD diagnoses, better stratification of patients in clinical trials, a new marker for treatment effect and insights into the pathophysiology and progression of AD in human patients.

Human connectomics is a scientific concept emerging in response to imaging advances. The Human Connectome Project (<http://www.humanconnectomeproject.org>) aims to combine imaging data from hundreds of participants to create a comprehensive circuitry map of the human brain and to link this to genetics and behaviour. Connectome studies of AD have already demonstrated abnormal functional connectivity between and within hemispheres. A recent genome-wide analysis of the connectome involved 366 twins scanned with MRI and high-angular resolution diffusion imaging to trace fibre tracts through the whole brain [64]. Significant associations between gene variants and connectivity were found in some fibre tracts, and the study was also important in indicating the relative contributions of genetic and environmental factors to brain connectivity.

Genome-wide association studies

Genome-wide association studies enable the automated analysis of the entire genome. Sequencing costs have plummeted by orders of magnitude during the past ten years, whereas levels of accuracy have increased. Common single nucleotide polymorphisms and other DNA variants significantly associated with disease can be identified. For example, nine genes newly associated with sAD through GWAS were mapped onto pathways linked to immune function, cholesterol metabolism and synaptic membrane processes, offering new angles for research and therapeutic intervention [65]. As susceptibility genes are catalogued and pathways are increasingly clustered, convergent nodes will be identified that could provide targets for new treatments.

The characterisation and reconstruction of molecular interactions related to GWAS-discovered genes for five complex disorders, including AD, suggested that susceptibilities converge on common molecular and biological networks [66]. In AD, unexpected significant relationships between immune function and growth factor signalling pathways were found. Other approaches are being developed to look for rarer novel variants and mutations, such as a pooled-DNA technique with next-generation, high-throughput sequencing and bioinformatics analyses, which found variants in *APP* and presenilins 1 and 2 that cause or increase the risk of sAD [67]. The deCODE Iceland study identified a low-frequency coding mutation in the *APP* gene that protects against AD, the first protective sequence variant found [68].

**FIGURE 1**

Likely information sources and data outputs in a new research paradigm using human-specific models to understand disease pathways. Data from 21st-century human *in vivo* and *in vitro* models, integrated and interpreted using systems biology and computer modelling, could help elucidate human disease AOPs (linking causes and effects for human diseases) from external factors through cellular changes to individual and population outcomes. This will help to create a systems-based understanding of complex diseases that so far has remained elusive. Black arrows indicate information sources, red arrows indicate data outputs. Abbreviations: AOPs, adverse outcome pathways; GWAS, genome-wide association studies; hiPSC, human induced pluripotent stem cells; omics, group including genomics, transcriptomics, proteomics and epigenomics.

In contrast to genetics, the tools used to discover environmental influences in disease have hardly progressed since the mid 20th century. A new concept to address this is the exposome, envisaged as the totality of a person's environmental exposures that can be characterised in an unbiased way by measuring all the external exposures (e.g. chemicals, drugs, radiation, infection, stress) that create internal toxins (e.g. produced by inflammation, oxidative stress, lipid peroxidation) in biological fluids, such as blood samples taken at different time points [69]. Exposome research could explore these nongenetic influences in AD, identifying early steps in an AOP for AD.

Systems biology and computational modelling

Computational interpretation, integration and modelling of different levels of human experimental data – molecular, cellular, tissue, organ, clinical and population – is a rapidly progressing approach for understanding complex, nonlinear biological processes. Current

research emphasises the discovery of single drug targets for which highly selective ligands are designed. But this strategy might be inadequate when the pathology is complex, as in AD. Many effective drugs act through effects on multiple proteins; systems biology research recognises a dynamic network of cellular pathways that could provide multiple targets for treatment [70].

A systems biology approach is essential for making sense of the data explosion resulting from omics studies, and can give a clearer understanding of cellular disease pathways and progression, as well as helping to identify sensitive and early biomarkers of drug efficacy. The complexity of human illnesses – such as cancer, cardiovascular disease and AD – demands a systems-based understanding, as does the integration of human molecular, cellular, physiological and environmental data to extend the concept of cellular pathways to the elucidation of disease AOPs (Fig. 1).

The NIH proposes developing quantitative and systems pharmacology (QSP) to advance drug discovery and development by

exploiting new knowledge of human cellular and tissue networks [71]. Using QSP to combine computational and experimental methods at multiple scales from biochemistry through to population levels is expected to result in less attrition in drug development, the discovery of new uses of existing drugs and novel tools for translating cell-level discoveries to tissues and to patients.

The development of small computational models of protein signalling pathways for major diseases, including AD, has shown that small-module systems analysis can be performed rapidly to generate new ideas to guide experimental research and to suggest new therapeutic concepts [72], whereas Tg mouse research is costly, time-consuming and oriented to single targets. AlzPathway, a publicly available map of signalling pathways, will help to evaluate candidate risk genes identified by GWAS and to analyse omics data [73].

Combining pathway analysis of GWAS data with composite memory scores in patients has highlighted pathways associated with memory impairment, demonstrating the potential of this technique to elucidate key targets in humans [74]. This study also thereby provided information for starting to build an AOP for AD. Bioinformatic analysis of networks identified by global gene expression profiling in AD brains is generating data about cell-level events in AD pathogenesis. Differential co-expression correlation network analysis of *APOE*ε4* and AD transcriptomic changes recently identified candidate core regulatory mediators related to sAD, and a gene variant that significantly affected amyloid deposition in human brain and AD age of onset of sAD. The results suggest a molecular pathway associated with *APOE*ε4* that promotes sAD [57].

Novel technologies are being developed for large-scale screening of protein–protein interactions and for following specific interactions in depth. In 2012, a transcriptional atlas of the adult human brain was generated, combining extensive histology and microarray profiling of about 900 brain areas, based on an analysis of the Allen Human Brain Atlas [75]. Anatomically precise, genome-wide maps of transcription patterns complement genomic sequence data and will help correlations of functional and genetic brain architecture.

Recently, data from diffusion tensor imaging and whole-brain microarray gene expression from a single individual have been analysed to identify connectivity between the hippocampi and the rest of the brain, as well as protein–protein interactions of relevance to AD in the same fibre tracts [76]. This showed that protein–protein interaction data can be related to measurable fibre tract deterioration in AD brains. Large, collaborative, longitudinal studies combining data from multiple technologies such as MRI, PET, CSF and blood biomarkers, genetics and neuropsychology are invaluable for understanding structural and functional connectivity and cognitive outcomes in AD research [77]. Systems biology developments provide, for the first time, a way to make sense of complex systems, such as AD and brain circuitry, with their nonlinear dynamics, multiscale organisation and emergent properties.

Concluding remarks

Animal studies remain dominant in the current paradigm for health research and drug discovery, yet costly and significant translational failures are acknowledged to be unsustainable. In

AD research, the focus on Tg mice continues despite their incomplete pathophysiology and unrepresentative etiologies, and a notable lack of evidence for their construct and predictive validity. If animal models are insufficiently predictive then disease and drug discovery research pursued within the traditional framework, with animal data playing a key part, will continue to disappoint. With the inevitable limitations of species variations, the quest for better animal models begins to seem outdated when a suite of advanced techniques could be applied to reliable human-specific models.

In toxicology, a structured and deliberate paradigm change is underway, moving away from animal testing and apical endpoints of toxicity towards a framework built more on advanced *in vitro* and *in silico* methods with a focus on human biology and AOPs. Thus, key aspects of the toxicology transition are the structured implementation of next-generation techniques and the shared understanding that animal use will decline, because better science is needed to make faster progress.

This review proposes that a similar change in conceptual thinking and research practice would benefit health research, argued here in the case of AD. Health research has an advantage over toxicology because the ‘gold standard’ human model is available with the technologies to use it. As discussed in this review, data from human *in vivo* and modern *in vitro* models, integrated and interpreted using systems biology and computer modelling, will elucidate human disease AOPs that link causes and effects from external factors through cellular changes to individual and population outcomes. This will help to create the systems-based understanding of complex diseases that so far has remained elusive, and which provides a core aspect of a new research paradigm.

A modern framework for disease modelling and drug discovery that rationally integrates important new and emerging techniques needs to be considered now. In-depth analyses of the limitations and advantages of animal models and of next-generation human-biology-based *in vitro*, *in silico* and *in vivo* methods could point to research funding and effort being directed away from efforts to improve animal models and towards the further development of non-animal methods. As in toxicology, the expectation would be for more cost-effective and more predictive data (than currently provided by conventional *in vitro* and animal studies), by reducing reliance on Tg mice, providing earlier human-relevant information and minimising late-stage drug attrition.

Considering change in a major paradigm of medical research is certainly a daunting task, but the probable advantages are substantial. For decades animal models have been seen as core to health research, but therapeutic progress has been slow, increasingly disappointing and costly. Emerging models and tools need further development and validation, but serious discussion and planning of a new framework for basic medical research and drug discovery should start now.

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the Field of Transplantation

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June 2, 2014

The Honorable Fred Upton
Chairman
Energy & Commerce Committee
U.S. House of Representatives
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Diana DeGette
Energy & Commerce Committee
U.S. House of Representatives
2368 Rayburn House Office Building
Washington, DC 20515

RE: 21st Century Cures - Policy Suggestions from American Society of Transplantation (AST)

Dear Chairman Upton & Congresswoman DeGette:

On behalf of the American Society of Transplantation (AST), representing the majority of professionals engaged in the field of organ transplantation, we applaud your ongoing leadership and steadfast resolve to strengthen our nation's ability to remain a leader in the field of biomedical research. The transplant community is grateful for the opportunity to be involved with the bipartisan Congressional 21st Century Cures initiative and appreciates the opportunity to contribute to this important process and dialogue.

AST is aware of the fiscal and political challenges that annually confront the federal funding process for the National Institutes of Health (NIH). Although consistent and predictable funding streams are without question key to the success of biomedical research, we also believe there are specific policy areas and partnerships that can be supported to enhance, expedite and advance new discoveries and cures. With this approach in mind, AST wishes to focus its comments today on a very important partnership that has served as a backbone and discovery engine for many successful biomedical breakthroughs.

Incentives for Entrepreneurial Investment in American Science

The AST is strongly supportive of the principle behind a Congressional program to advance the future of medical research in America for the 21st Century. We are also very grateful for the opportunity to participate in the early steps of this initiative by introducing some ideas for consideration now. But we also wish to emphasize that we recognize this is just the start of the process and look forward to participating in its evolution.

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WORLD TRANSPLANT CONGRESS 2014

July 26-31, 2014
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Page Two

We continue to believe that one part of the solution to making sure the medical research infrastructure of our country remains strong and competitive in a dynamic world is to continue support for the National Institutes of Health. The last decade of essentially unchanged NIH funding in the face of significant increases in the costs of doing science fueled by a literal explosion of new and very exciting technologies has significantly eroded the competitive position of the US and driven many young, promising scientists to other fields. But even more concerning to the AST has been the significant erosion in the ranks of physician/scientists, the leaders in our medical institutions that choose to pursue both laboratory research and clinical medicine. Unfortunately, as NIH funding rates for new grants has continued to fall these physician/scientists are forced out of research by the powerful winds of health care reform and institutional pressures to earn their salaries doing clinical care. The result is abandoning the translational medical research that has brought the cures for disease to patients and written the history of medicine.

The AST proposes a novel solution to this challenge for consideration that we call “entrepreneurial science”.

We note that this solution is not based on demanding additional funding for NIH. While we are certain that Congress would increase NIH funding if that was possible, a pragmatic view of the last decade and the current fiscal realities dictates that we need to change course if we want to succeed in maintaining our place. The AST believes we need to propose and operationalize novel ways to support the future of medical research by capitalizing on the many strengths of the US economic system to create new funding opportunities. Thus, entrepreneurial science starts at the interface between basic laboratory research and clinical trials. The objective is to take promising new therapies or diagnostics based on the latest technologies like deep DNA sequencing, tissue engineering and gene therapy and successfully translate them into tomorrow’s cures. We propose the exploration of creating new ways to foster connections between basic scientists and physician/scientists with our nation’s venture capital and investment banking communities. The entrepreneurial spirit of our country has been a core strength since its founding and we simply wish to tap into this spirit again to create the opportunities for translating the latest scientific research into the latest cures and advance the health and safety of the American people.

First, it is critical to state that there is no future for medicine if we don’t support basic laboratory research. Basic medical research creates the opportunities for translation to clinical medicine. This will remain a primary mission for NIH funding. But when basic research is translated successfully to clinical medical practice it generates huge opportunities for new companies to be created with venture investment. That potential is the basis of entrepreneurial science.

However, the truth is that the majority of physicians and scientists in the US do not have the training or the time or access to the support infrastructure to really facilitate the full transition from laboratory to bedside to a commercially viable product. But only when that full transition is made successfully are our patients actually able to benefit from all the work. In other words, too much great basic and translational research is funded with precious NIH resources, published in our best scientific journals and still never actually benefits a patient. One practical reason is that we don’t have enough expertise available in many of our nation’s universities and medical centers to finish the job. Another reason is that the physician/scientists that have done this work want to go back to the laboratory and concentrate

Page Three

on making the next discovery rather than start the risky and difficult process of translating the work to clinical practice, dealing with the FDA and trying to obtain the considerable funding required to make clinical translation possible. But even in systems with some resources for such entrepreneurialism the current reality is that there are few incentives for scientists and physicians to risk the enormous time and energy required to do this translational work especially when at this time of such limited funding the failure to get their next NIH grant means ending their life's work.

Therefore, entrepreneurial science as a new endeavor must take advantage of creating pools of capital and expertise to invest up front in promising basic research with the agreement that the investors will also have access to commercializing these advances along with the Universities and Medical Centers involved. This is not intended as a passive process but rather an active collaboration between these physicians and scientists with experts in translating science to practice and commercializing it successfully. In this system, promising science would be presented to these teams of translational, commercial and investment experts very early in development as a competitive and managed grant process. Then decisions would be made to join in collaboration with academic physicians and scientists to take their discoveries through the full cycle to a new medicine, diagnostic test or therapeutic strategy. A key point is that these teams can be formed from existing biotechnology and pharma work forces and would instantly be a unique resource to our nation's scientists and also be able to tap into streams of capital from big pharmaceutical companies interested in the science as it develops and shows promise.

We recognize that there are many details to consider to fully develop our proposal for entrepreneurial science. But we also have enormous confidence in the power of the American spirit of entrepreneurialism and simply wish to bring it to medical research now at a time that our nation's leaders realize the critical importance of this work to the future health of all Americans.

The AST represents thousands of physicians and scientists that have dedicated their lives to caring for patients, advancing the practice of transplantation and medicine, and making the scientific discoveries that will create the future cures. We look forward to working with Congressional leadership to understand the details and then operationalize what is now just an aspirational concept of a novel opportunity to fund the next generation of medical miracles with entrepreneurial science.

If you have questions or require any additional information, please do not hesitate to contact me directly or the AST Government Relations Directors, Bill Applegate and Chris Rorick, at [REDACTED]

Sincerely,

[REDACTED]
Daniel R. Salomon, MD
President

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June 1, 2014

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**NASPGHAN Annual Meeting &
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October 22-25, 2014
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The Honorable Fred Upton
Chairman
Energy and Commerce Committee
U.S. House of Representatives
Washington, D.C. 20515

The Honorable Diana DeGette
U.S. House of Representatives
Washington, D.C. 20515

Dear Chairman Upton and Congresswoman DeGette:

On behalf of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), I thank you for your leadership and commitment to advancing biomedical innovation and getting new treatments to patients more quickly. We applaud the launch of the 21st Century Cures Initiative and welcome the opportunity to be part of the dialogue. We therefore are pleased to offer the following thoughts in response to your first white paper, "21st Century Cures: A Call to Action" and look forward to working with you.

With more than 1,500 members, NASPGHAN is the leading society in the field of pediatric digestive diseases. NASPGHAN's mission is to improve quality of care and health outcomes for infants, children and adolescents with disorders of the gastrointestinal tract, the liver and nutritional conditions by promoting advances in clinical care, research and education.

What we hope to convey in these initial comments is that many aspects of the discovery, development and delivery process are unique to pediatrics. We therefore strongly encourage you to consider a future white paper and hearing or roundtable that specifically addresses issues associated with bringing drugs, devices, and other medical therapies to pediatric patients. NASPGHAN values its partnerships with the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) and supports their missions to advance research and to ensure the safety and efficacy of new and promising treatments. Still, barriers exist that hamper innovation and patient access to promising therapies. In these comments, we hope to shed light on some of these barriers as a basis for a future dialogue with you.

Innovation

The NIH is the central driver of innovation in this country, particularly in academic centers. Yet, the biggest barrier to innovation is the lack of adequate federal funding for biomedical research. Even though the scientific and public health need is great, the NIH budget has dropped 22 percent (\$6 billion) since 2003 when accounting for inflation. A decade ago, the NIH funded nearly one out three grant applications. In

FY 2013, the NIH success rate was 16.8 percent. As NIH Director Francis Collins, MD described at an April 2, 2014 Senate hearing, “We are not limited by ideas, we are limited by resources.” We ask Congress to commit to increasing the NIH budget starting with a \$2 billion increase to the NIH budget in FY 2015 for a total funding level of \$32 billion. We also urge Congress to consider the impact of budget instability, including the effect of sequestration and budget cuts, on our nation’s researchers. An increase in the NIH budget must be accompanied by a stable trajectory of funding that will instill confidence in our research workforce, otherwise we risk losing a generation of scientists, as well as academic physician investigators, who are so vital to taking research from bench to bedside.

Last year, NASPGHAN released an updated pediatric gastroenterology research agenda which includes six key clinical categories: inflammatory bowel disease, functional and motility disorders, liver disorders, pancreatic disorders, allergy/intestinal failure/infection, and nutrition disorders. There are so many unanswered questions that remain in each of these areas and for which research is so desperately needed.

Regulatory Issues

Along an increased federal investment in medical research, maintaining our country’s leadership in innovation requires a regulatory structure that promises safety and efficacy of drugs, devices, and therapies. The FDA is the government agency charged with evaluating safety and efficacy of drugs, and also ensuring the safety of patients who are enrolled in clinical trials. Over the last 15 years, the FDA has expanded its oversight greatly. Now, the FDA is actively regulating not only industry sponsored studies aimed at bringing drugs to market, but also small scale studies being conducted at academic medical centers. The process by which academic investigators now need to conduct interventional studies involves applying for an “investigational new drug” (IND) application and submitting reports similar to industry. The same pathway used for industries trying to get a new drug to market is being applied to physicians who want to study an old drug in their clinics or practices. The regulatory paperwork is a time-consuming process that cannot be easily overcome by academic researchers, especially for pediatric studies. Unlike companies with large budgets and regulatory departments, academic investigators have limited time and resources. Therefore, many of our talented young investigators are choosing to abandon interventional studies altogether, or to leave academia for industry where they have the resources to go through the FDA process. Innovation at a “grass roots” level is discouraged.

Recently, the FDA has developed draft guidance for clinical researchers for determining whether human research studies can be conducted without an IND application. In this guidance, even foods that are being studied to treat diseases may soon be required to file IND documents with the FDA. In the guidance, the FDA broadened its interpretation of when an IND is required for a food study, including studies related to infant formulas and probiotics. As NASPGHAN has conveyed to the FDA, its draft guidance establishes that an individual academic researcher who wants to study whether a dietary change may treat a specific condition (e.g., malnutrition or allergic colitis), now has the same IND responsibility as a drug company developing an investigational drug.

Very few academic physicians want to make labeling claims, including those for foods or dietary supplements. Researchers at universities have limited interest in marketing claims, or profits. They simply want to know if a treatment works. Such studies gather more formal data on interventions that are commonly being used in clinical practice. Researchers with access to limited research dollars cannot risk study delays and otherwise unanticipated added study requirements. If the FDA desires to regulate all academic investigational trials through the IND mechanism, NASPGHAN has encouraged the FDA to consider the limited resources academic investigators have and work closely with such investigators to simplify the IND process. The pediatric gastroenterologists within NASPGHAN will gladly partner with

FDA to educate the academic community about clinical research and about the regulatory pathways that serve as the foundation to protect the safety of the U.S. clinical trial participants.

Access to Medications for Children

In considering urgent changes that are needed so children under 18 years of age can access new therapies already proven to work in adults, we suggest evaluating the current mechanisms by which drugs are tested and approved in children under 18 years. Currently, in order for a new drug to be approved for pediatric use, the current regulatory pathway requires that separate, phase 3 pivotal pediatric trials be performed to demonstrate safety and efficacy in children. The consequence has been that after a drug is FDA approved, licensed and available to adults with the same disease, it can take more than a decade until the drug is tested for children suffering from the same condition. As an example, the only drugs FDA approved for treatment of irritable bowel syndrome (a very common pediatric disorder) have only been approved for use in adults, despite one of these drugs having been on the market for more than six years.

In 1982, the FDA published a statement on “off-label” use of medications (see Appendix 1) that, to the best of our knowledge, has not been updated. The FDA statement wisely concluded that “‘unlabeled’ uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature.” In other words, drugs approved in adults could be utilized in children if medically appropriate. Recently, however, insurance companies have begun denying the use of newer drugs in that have been proven to be effective in patients over 18 years to patients under 18 years on the grounds of “off-label use,” even though the FDA does not state such use is inappropriate. Physicians must then go through an elaborate process of appeals to get the medication for their patients.

The end result of this current state of affairs has been the emergence of a two-tiered health system. Those families with resources will find physicians with the skill set to use these medications off-label, often times at great expense to families since insurers often consider such use as “experimental” and not covered. Those without such access to care continue to suffer without these therapies. Therefore, the most vulnerable of our children remain at greatest risk.

It is important to note that while the current system emerged out of an “abundance of caution” for our children, it is rooted more in emotion than science. For many conditions, the biology of the disease is similar whether an individual is six or 60 years old—although the severity of the condition is often most impactful on the young necessitating a greater need for newer therapies. Also, using 18 years of age as a division between pediatric and adult drug development has its roots in law and not physiology. We would propose that along with adult drug development, new agents undergo phase 2 testing in young patients to establish dose-exposure relationships. Phase 3 trials that demonstrate efficacy can proceed and pediatric efficacy can be extrapolated from adult data. Having established the dose-response from pediatric phase 2 testing, an approval pathway with known pediatric dosing can then go forward for agents with disease-specific proven efficacy.

The remaining issue will be establishing pediatric safety. The current state of drug delivery is that once a drug is available, there is an off-label pediatric use that often outnumbers any given number of subjects that have been included in phase 3 pediatric trials. Rather than capturing this real-world potential repository for long-term pediatric safety, the data go uncollected. It is proposed that pediatric safety continue to be partly inferred from phase 3 testing, as is the current practice. Pediatric specific safety issues have always been best established through post-marketing surveillance. As such, the suggested pathway should also require drug companies to establish and maintain a well-designed, long-term patient

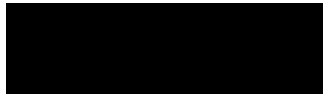
outcome registry. This would be a more effective expenditure of drug company resource investment than a separate, likely small, pediatric phase 3 trial and, in this way, rare pediatric specific events can be captured.

Conclusion

Over the past four decades, major breakthroughs and achievements in basic biomedical science have supplied unprecedented potential information for improving human health. The need for properly designed and conducted pediatric clinical trials and pathways to encourage individual investigator-initiated research has never been greater. We hope the 21st Century Cures Initiative will prominently feature children, help encourage innovation, and speed the delivery of new treatments to pediatric patients. Our organization, NASPGHAN, is pre-eminent pediatric professional organization focused on the treatment of children with digestive and liver diseases. As the voice for pediatric digestive health, we look forward to serving as a resource to you as you continue your mission to improve our nation's health care.

NASPGHAN appreciates consideration of our comments, and we hope that you will look toward our organization as a resource on this issue. Please contact NASPGHAN's Washington representative, Camille Bonta, at cbonta@summithealthconsulting.com or (202) 320-3658 should you have any questions or desire additional information.

Sincerely,



Athos Bousvaros, MD

President

North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

Appendix 1

April, 1982, FDA Drug Bulletin
re: "Use of Approved Drugs for Unlabeled Indications"

Department of Health and Human Services
Public Health Service Food and Drug Administration, HFI-22
Rockville, Maryland, 20857
FDA Drug Bulletin: Information of Importance To Physicians and Other Health Professionals

April 1982, Volume 12 Number 1, Pages 4-5

"Use of Approved Drugs for Unlabeled Indications"

The appropriateness or the legality of prescribing approved drugs for uses not included in their official labeling is sometimes a cause of concern and confusion among practitioners. Under the Federal Food, Drug, and Cosmetic (FD&C) Act, a drug approved for marketing may be labeled, promoted, and advertised by the manufacturer only for those uses for which the drug's safety and effectiveness have been established and which the FDA has approved. These are commonly referred to as the "approved uses." This means that adequate and well-controlled clinical trials have documented these uses, and the results of the trials have been reviewed and approved by the FDA.

The FD&C Act does not, however, limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. Such "unapproved" or, more precisely, "unlabeled" uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature.

The term "unapproved uses" is, to some extent, misleading. It includes a variety of situations ranging from unstudied to thoroughly investigated drug uses. Valid new uses for drugs already on the market are often first discovered through serendipitous observations and therapeutic innovations, subsequently confirmed by well-planned and executed clinical investigations. Before such advances can be added to the approved labeling, however, data substantiating the effectiveness of a new use or regimen must be submitted by the manufacturer to the FDA for evaluation. This may take time and, without the initiative of the drug manufacturer whose product is involved, may never occur. For that reason, accepted medical practice often includes drug use that is not reflected in approved drug labeling.

With respect to its role in medical practice, the package insert is informational only. FDA tries to assure that prescription drug information in the package insert accurately and fully reflects the data on safety and effectiveness on which drug approval is based.

June 1, 2014

Enhancing the Ability of Biopharmaceutical Companies to Discover, Develop, and Deliver 21st Century Cures

There may be no higher public health priority than accelerating the ability of researchers to navigate the long and costly discovery and development process to deliver new medicines and potential cures to patients in need. For this reason, the Pharmaceutical Research and Manufacturers of America (PhRMA) strongly supports the Energy and Commerce Committee's initiation of the 21st Century Cures project under the leadership of Chairman Fred Upton and Representative Diana DeGette. PhRMA thanks the Committee for the opportunity to submit comments on the Committee's white paper entitled, "21st Century Cures: A Call to Action."

PhRMA is a voluntary, non-profit association that represents the country's leading pharmaceutical research and biotechnology companies. PhRMA members are dedicated to developing medicines that allow patients to live longer, healthier, and more productive lives. In 2013 alone, PhRMA's member companies invested an estimated \$51.1 billion in the research and development of new medicines.

SUMMARY OF PhRMA'S RECOMMENDATIONS

PhRMA appreciates the opportunity to offer recommendations to achieve our shared goal of accelerating the discovery, development, and delivery of treatments and cures to patients.

In the discovery phase, PhRMA supports

- Robust funding of the National Institutes of Health (NIH) as well as more collaborative efforts within NIH;
- Pre-competitive efforts in the discovery phase of drug development; and
- Investments in a strong science and regulatory workforce.

In the development phase, PhRMA supports

- The development of new, innovative clinical trial networks;
- Enhanced collaboration between government agencies, the biopharmaceutical industry, and academia to transform the clinical trial ecosystem;
- The use of real-world evidence and observational data to establish the benefit of a drug;
- A regulatory environment that promotes the use of biomarkers and companion diagnostics; and
- A regulatory review process that recognizes patient reported outcomes as essential to understanding treatment benefits.

In the delivery phase, PhRMA supports

- Modernization of the Food and Drug Administration's (FDA) regulation of communications with healthcare professionals to ensure that companies can share

Comments on the 21st Century Cures: A Call to Action

truthful, scientifically accurate, and data driven information in order to improve patients' health outcomes;

- Programs and arrangements that support adherence to prescribed drug regimens;
- Ensuring that new payment models within Medicare allow for appropriate adoption of and access to medical advances and ensuring that those models do not undermine the successful Part D program;
- Advancing reliance on robust quality measures – including measures of clinical outcomes and patient reported outcomes -- in new “value-based payment” models;
- Strengthening health information technology systems to ensure standards are transparent and keep current with innovation, and enable innovators to serve as research partners with other stakeholders via balanced access to electronic real-world data sets; and
- Ensuring that appropriate transparency and standards are in place when medical evidence is communicated to providers by public agencies or under public programs.

In addition, robust intellectual property (IP) protections are critical to incentivizing the substantial investments needed to fuel the discovery and development phases as well as to provide the potential to recoup the investments made and earn a potential return when the medicines are delivered to patients, providing the ability to fund future research. PhRMA supports strong protections for intellectual property rights, including patent and data protections, in the United States and abroad.

PhRMA is committed to working with the Committee to pursue these proposals and is happy to discuss further details with the Committee.

DISCOVERY

Drug Discovery

As medicine evolves into more individualized therapies, the efficient, timely, and effective discovery and development of these highly specialized medicines is a crucial part of the healthcare delivery system. We support Congress' commitment to providing robust resources to the NIH. We also call for more effective collaborative efforts within NIH institutes and centers to ensure the groundbreaking basic research done at the NIH is shared and translated into practical applications for the ongoing medical research, discovery, and development done in the private sector.

To this end, we favor pre-competitive efforts in the discovery phase, including the following:

- Target validation, including the continued support of the Accelerating Medicines Partnership;
- Predictive animal efficacy models;
- Novel approaches to develop combinations of medicines, medicines with devices, and medicines with companion diagnostics; and
- Use of current regulatory authority to streamline approaches to proof-of-concept in humans.

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Congress should ensure investment in training, recognizing, and rewarding scientists and physician-scientists in drug discovery/development and regulatory science with funding from government and other sources. It is also imperative to develop a cadre of experts skilled in experimental medicine.

DEVELOPMENT

Global Clinical Trials Networks

Preserving the sustainability of clinical research while maintaining high standards is essential to the future of biomedical innovation and public health. The fragmented U.S. clinical trial ecosystem is facing many challenges, including increasing costs, reduced funding, a shortage of clinical trial participants and qualified investigators, and a fragmented and antiquated infrastructure. Biopharmaceutical companies have put forth great efforts to address a number of operational challenges in clinical trials, both individually through internal improvements and more recently through participation in broad industry initiatives. While such efforts are making strides, there is a need for a coordinated transformation of the clinical trial ecosystem to accelerate translation of scientific knowledge into new health solutions for patients.

Congress should encourage government agencies, the biopharmaceutical industry, and academia to work together on the following concepts to drive such transformation:

- Increasing public awareness about the importance of participation in clinical trials;
- Building connectivity across stakeholders in the clinical trial ecosystem through the creation of permanent physical or virtual networks to increase participation by diverse patient populations, particularly by underrepresented groups (e.g., ethnic minorities, pediatric patients);
- Accelerating regulatory efforts to support globalization and modernization of clinical trials (e.g., new clinical trial design, harmonization);
- Developing a competent and culturally sensitive clinical trial workforce; and
- Accelerating progress in translational research and training through collaborations between government, industry, and academia.

Congress should support policy enhancements that can facilitate and incentivize multi-stakeholders collaborative efforts to advance these objectives.

Real-World Evidence & Use of Observational Data

The real-world use of medical products generates volumes of valuable information, and although the FDA has demonstrated its ability to make important safety-related decisions based on real-world evidence, that evidence is generally not used to evaluate the benefits of a drug. New indications for a product that has already demonstrated safety and efficacy for another use are most often approved based on additional randomized controlled trials, which require significant time and resources.

We support expanding FDA's ability to make decisions regarding therapeutic benefit based on real-world evidence used as a supplement or potentially as a replacement for randomized controlled trials, as appropriate. This proposal would require modest policy changes to broaden

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the application of the existing approval framework and could be implemented in a step-wise fashion.

Enabling greater use of real-world evidence would have significant benefit for patients and other stakeholders in the healthcare ecosystem. As real-world evidence increasingly informs healthcare decisions, it will be important to ensure that a broad range of stakeholders have equal access to these data and that sound, rigorous research methodology is in place for data collection and analysis. Policy reforms are needed to ensure all partners can appropriately access data sets that will support innovation.

Biomarkers and Companion Diagnostics

Biomarkers provide a dynamic and powerful approach to understanding the entire spectrum of a disease, from the earliest symptoms to terminal stages. By conducting research in this space, researchers can continue focusing their efforts and resources on the most effective therapies, thus reducing the time and cost to bring a new therapy to market and eventually to patients. To ensure the adoption of these innovative and modern tools, Congress should support a regulatory environment that promotes a smooth translation of these tools from research to practice.

To ensure that effective treatments reach patients in a timely manner, the regulatory environment must adapt to the new scientific and technical challenges related to the development and use of biomarkers and diagnostics.

Patient Reported Outcomes and Patient-Focused Drug Development

Although improving survival remains a key target for much of drug development, finding new treatments that improve how the patient feels or functions is an increasingly important goal. Patient reported outcomes (PROs) complement traditional clinical measures such as length of survival, measures of disease, and physiologic markers. To advance progress towards patient-focused drug development, there is an immediate need for an efficient regulatory review process that allows new validated PRO measures to be included in drug trials where patient input is essential to understand treatment benefits.

It is important to advance scientific processes and tools by which patient information and perspective is gathered. Existing technology can be leveraged to gather robust, dynamic, and patient-driven data to inform all stages of development and facilitate regulatory review.

DELIVERY

Modernize FDA's Regulation of Healthcare Communications

While most patients may not be aware that the FDA highly regulates the medical and scientific information that biopharmaceutical companies may share with healthcare professionals, the FDA's regulations have a direct impact on patient care. Patients expect that their medical professionals receive the latest scientifically accurate and data-driven information about the medical treatments they prescribe. Unfortunately, the FDA's regulations regarding companies' ability to share truthful, non-misleading medical and scientific information are outdated. These regulations do not even mention the Internet, much less facilitate or allow robust use of social media in a manner akin to the FDA's own use of such communication tools.¹

The FDA's restrictions on communication about medically accepted new uses of approved medicines should be revisited in order to provide all healthcare professionals, including those in rural areas, with scientifically accurate, data-driven information that can help patients.

To get the best possible health outcome for patients, Congress should press the FDA to revise its regulations to allow companies to share truthful, scientifically accurate, and data-driven information with healthcare professionals to inform treatment decisions, including the following:

- Analyses of real-world medicine usage based on actual patient records;
- Pharmacoeconomic information that can inform patient treatment decisions;
- Subpopulation information from clinical trials, including specific information relating to the effects of medicines by race or gender;
- Observation and comparative data information from the use of a medicine outside of randomized clinical trials; and
- Information on medically accepted alternative uses of medicines.

FDA's regulatory structure should facilitate full and robust communication about truthful, non-misleading scientific and medical information, including information sourced from outside of a medicine's package insert.

Promote Programs in Support of Appropriate Use of Medicines

Research establishes that proper use of medicines yields improved health outcomes, while treatment gaps and lack of adherence to physician prescribed treatment with medicines lead to higher spending on otherwise avoidable medical care. Given the value of appropriate use of medicines, including adherence to prescribed therapies, policy reforms should support programs and arrangements that support adherence to prescribed drug regimens.

Medicare Payment and Delivery Reform

In Medicare, moving to alternative payment models (APMs) that put providers at risk for cost containment threatens to undermine incentives for innovation and patient access to new treatments. To protect against these risks, Congress should ensure that new payment models incorporate mechanisms, such as a "pass-through" payment modeled on existing policies that exist in the Medicare Outpatient Prospective Payment System, that allow for appropriate adoption of and access to medical advances.

In addition, Congress should ensure that patients are informed of and have access to the full range of appropriate treatment options in new payment models. This includes protecting access to medically accepted off-label alternative uses of approved drugs and biologics that are included in recognized compendia and peer-reviewed literature based on existing statute. Complementing regulatory policies noted above, CMS should also ensure that any companion diagnostic products approved by FDA as part of labeling of a targeted therapy should automatically qualify for Medicare coverage along with the drug or biologic.

As these reforms evolve, a transparent and predictable process and basic protections for patient access and continued innovation must be in place. Currently, the CMS Center for Medicare and Medicaid Innovation (CMMI) operates with only limited transparency and accountability.

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Reforms are needed to improve the process for developing and evaluating alternative payment models at CMMI to significantly increase transparency and predictability in development, testing, and evaluation of APMs. Congress should push for the following reforms:

- Require CMS to establish, via rule making, criteria it will use to evaluate selection of alternative payment models for testing and expansion;
- Ensure adequate transparency and input by allowing for public and stakeholder input on potential new payment models before they are tested by CMS and create a patent-focused national advisory committee to evaluate Medicare APMs; and
- Strengthen existing protections that ensure CMS will not unilaterally change existing statute in national, permanent payment reforms.

Further, Congress should require CMMI to ensure that new Medicare payment models include a sufficiently broad number of clinical quality measures and to link these measures to financial incentives.

Lastly, Congress should ensure that APMs do not undermine the successful Part D program.

Provider Quality/Value-Based Purchasing

Quality measurement and public reporting are the cornerstone of healthcare provider and health plan evaluation. As quality measurement matures and continues the shift from a reporting exercise to “pay for performance” or “value-based payment” (VBP), ensuring that measures are correctly evaluating quality of care and health outcomes becomes increasingly important. If measures fail to recognize the value that innovation brings to patients, that value will not be supported and innovation will be discouraged.

To ensure VBP programs provide a complete, current picture of care quality, Congress should ensure that measures are maintained regularly so that they keep pace with the evolving scientific evidence base and current standards of clinical practice. Measure developers must have appropriate processes in place to evaluate new evidence and keep their measures up-to-date. Mechanisms must be in place to ensure that new diagnostics and pharmaceutical advances are incorporated into quality measures in a timely manner so that the measures do not become a hindrance to innovation or the introduction of new products.

Furthermore, the breadth of measures applied in new payment models must provide a comprehensive picture of the quality of patient care and enable evaluation of the range of relevant clinical and patient-reported outcomes. Measures should be developed, endorsed, and implemented through transparent processes, and incentives applied to measure performance achievement should ensure that quality of care does not decline or prohibit the provision of care.

Health Information Technology

To ensure policies related to health information technology (HIT) and real-world evidence support an environment of continued innovation, policymakers must consider ways to ensure that the development of HIT systems is transparent and continuously updated, while also ensuring broad stakeholder access to real-world evidence and sound methodologies to support its use.

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To realize this potential, Congress should ensure that HIT systems, such as electronic health records (EHRs), be maintained regularly to reflect currently available clinical evidence. EHRs use basic clinical information as the foundation for important tools such as electronic prescribing, formulary and benefit information, drug-drug interaction alerts, and clinical decision support. Empowering patients and physicians with EHR information that is high quality, evidence-driven, and regularly maintained, while providing transparency around this information, will help ensure that our healthcare system harnesses innovation and delivers the best possible results for all patients.

Evidence Evaluation and Communication

While patients and consumers need quality information to support their healthcare and medical decisions, it is important to ensure that appropriate transparency and good standards are in place when evidence is communicated to providers by public agencies or under public programs. Congress should establish patient protections to ensure that communication of evidence, including comparative effectiveness research findings, do not interfere with doctor-patient decision-making or discourage patient access to the full range of available tests or treatment options.

Intellectual Property: Fueling Drug Discovery, Development, and Delivery

The process of innovation is very complex, lengthy and fragile in nature. Recent biopharmaceutical advances—driven by scientific research and creative genius—would have been impossible without a system of laws that provide the structure, stability, and competition needed to foster the R&D investments required to bring new medical breakthroughs, including cures, to patients. In order to continue to foster the much-needed research into medical breakthroughs that will save lives and lower overall healthcare costs, we must ensure robust IP rights, including the following:

- Policies to ensure well-functioning patent systems in the United States and abroad, including support for comprehensive patent rights and adequate remedies for enforcement of patents;
- Fair protection in the United States and abroad for data generated by companies to demonstrate that medicines are safe and effective, which includes policies to prevent unfair commercial use by third parties of the substantial data generated by companies; and
- Targeted proposals to incentivize R&D where market incentives may be inadequate to address specific medical needs.

To advance the discovery and development of new medicines, Congress should ensure that the data protection period is long enough to allow innovators, who undertake the costly and uncertain R&D process, to earn a positive rate of return. As provided in the Biologics Price Competition and Innovation Act, Congress should continue to affirm the 12-year period of data protection for innovator biologics.

In addition, because biopharmaceutical patents cover products that take a long time to develop, significant portions of the patent term for a new medicine are lost before it enters the market. The ability for generic drug companies to challenge patents as soon as four years after a brand medicine enters the market further compounds patent term losses and creates uncertainty. As a

Comments on the 21st Century Cures: A Call to Action

result of challenges occurring earlier and more frequently, the average effective patent life until there is a generic version of a new medicine on the market is just 12.6 years. Industry dynamics including, but not limited to, the availability of venture and other forms of private capital, a gap in highly skilled workers, and biopharmaceutical competition have evolved considerably since Congress passed the Hatch-Waxman Act in 1984. As a result, there have been dramatic increases in rates of generic penetration and patent litigation, declines in the availability of venture capital, and challenges in finding workers with the STEM skills needed. These and other changes in the environment have resulted in increased uncertainty for companies, suggesting that the 5 years of data protection provided for small molecule drugs may be insufficient. Ultimately, Congress should support strong patent and data protections that are critical to ensuring a favorable environment for continued R&D investment in the United States and assess whether current incentives, including but not limited to IP incentives, are sufficient to stimulate continued medical innovation.

ⁱ See, e.g., FDA, “#FDA approves #Cytamza for stomach cancer” available at https://twitter.com/FDA_Drug_Info (Apr. 22, 2014).

Comments from Varian Medical Systems

21st Century Cures White Paper: A Call to Action

June 1, 2014

Varian Medical Systems applauds the work of Chairman Fred Upton, Congresswoman Diana DeGette, and the members of the House Energy and Commerce Committee for undertaking the 21st Century Cures Initiative. Varian has a long history of innovation and is pleased to offer comments for the Committee's consideration. We would like to provide examples of how Varian, as a private sector company, has successfully harnessed government funded research investments over the years to develop life-saving 21st century technologies for patients.

Varian was founded in 1948 by Russell and Sigurd Varian who were scientific inventors with a shared goal of improving people's lives through medical innovation. One of the first high-tech companies in Silicon Valley, Varian is a true great American success story that has continually pioneered advancements in medical technology while maintaining our core commitment to improving patient health.

Since the company's inception, Varian Medical Systems has grown to become the world's leading producer of medical technology and software for treating cancer with radiation therapy, radiosurgery, proton therapy, and brachytherapy. Varian's technology provides hospitals and clinics around the world with the most advanced tools they need to treat thousands of cancer patients each day. Our two principle production lines are oncology systems and imaging component products.

Varian's mission is to save 100,000 more lives each year from cancer. We strive to achieve this goal by continuing to innovate even through challenging economic times and uncertain political environments. Our products are designed both for today's patients and for the health care delivery system of the future.

Continuous innovation is critical to effectively treating and curing cancer and other chronic conditions. Varian's commitment to keeping patient needs first is at the heart of our company's mission. If we are successful, cancer will transition to a manageable disease that allows for positive patient outcomes with consistent treatment, similar to heart disease and diabetes. The goal is ambitious, but necessary if we are going to achieve new breakthroughs for patients.

Varian's mandate is to investigate the development of new, disruptive, breakthrough technologies that will create significantly improved capabilities for Varian's customers. Varian's internal research institution responsible for driving innovation is the Ginzton Technology Center, or GTC. The GTC was formed in 1999, but has existed under various names since the 1960s, when it was known as the Varian Research Center. Named for Edward Ginzton, one of the founders of Varian, the GTC serves as our central research and development organization, incubating new technologies, supporting product development for the company's business units, and conducting government or industry-sponsored research projects. GTC advocates for an environment where top researchers could innovate, for the benefit of humanity, in an environment without the boundaries of a traditional business unit, and that spirit still exists at Varian today.

One of the best examples of a technology that GTC researchers helped develop into a commercial product is the digital flat-panel X-ray imager. This technology is revolutionizing the use of X-ray imaging both inside and outside the medical community. Technology specifically developed at Varian makes it possible to obtain high-resolution radiographs, real-time X-ray movies and even CT scans from the same camera. It also gives X-ray imaging unprecedented portability and environmentally friendly

filmless processing which is helping to substantially broaden the technology's range of applications.

Our team worked with researchers from Xerox's Palo Alto Research Center in the early 1990s to repurpose technology original developed for copy machines into a format suitable for X-ray imaging. Prior to this development, many believed this technology would either be too expensive, too low in resolution or not robust enough for use in radiation oncology and diagnostic imaging. Thanks to the researchers at Varian, we were able to transform this technology into an FDA cleared product that provides substantial benefits to patients and clinicians.

Today, we manufacture a very advanced version of this flat-panel imager in our Salt Lake City facility, where, along with our employees manufacturing CT tubes, we employ nearly 700 people. It is important to note that the roots of this groundbreaking technology began with a partnership with the federal government in the form of a Defense Advanced Research Projects Agency (DARPA) grant.

Varian is extremely supportive of government funding opportunities for medical research, both for basic scientific research and also for research that has the opportunity to improve and advance products and procedures already on the market. We support expanded opportunities for

the government to fund more device translational research as well as research that shows the promise of drug and device synergies.

Varian is also participating in research partnerships with both educational and private institutions throughout the country. Some of our most exciting technological advancements have emanated from our partnerships with universities. For example, one of the latest cancer treatment methodologies to improve the treatment of lung cancer without invasive surgery was developed in conjunction with an academic partner. Varian currently benefits from a National Institutes of Health/National Cancer Institute funded Academic-Industrial partnership with Stanford University to develop novel high energy x-ray detectors for purposes of improving treatment planning for radiotherapy. More projects like this are possible with continued funding and expansion of the NIH/NCI academic-industrial partnership program.

The combination of private and public-sector dollars will be exponentially valuable to tomorrow's patients. Varian's research success over the years can and should be replicated by other companies to develop 21st century cures for patients. Thank you for the opportunity to comment on this critical relationship between private sector innovation and

government support and we look forward to working with the Committee as they examine ways to strengthen this partnership.

June 02, 2014

2183 Rayburn House Office Bldg
United States House of Representatives
Washington, D.C., 20515

Dear Chairman Upton and Representative DeGette,

The Endocrine Society appreciates the opportunity to respond to the questions posed by the “21st Century Cures: A Call to Action” whitepaper. Founded in 1916, the Endocrine Society is the world’s oldest, largest, and most active organization devoted to research on hormones and the clinical practice of endocrinology. Our membership includes over 17,000 researchers and clinicians working to discover, develop, and deliver new cures and therapies to patients worldwide. We are therefore encouraged by the new 21st Century Cures Initiative and support your efforts to optimize the biomedical research cycle.

The Endocrine Society would like to emphasize that administrative tasks in the conduct of research represent an increasing burden on investigators. Furthermore, excessive administrative workload wastes critical taxpayer dollars and delays the conduct and completion of life-saving research by increasing the amount of time investigators must spend writing grants. Uniform templates for grant applications and reports, which require minimal formatting, would save time without reducing information content. Automated data transfer between PubMed Central and eCommons—including the RPPR grant reporting system—would eliminate unnecessary duplication of effort.

Additional potential solutions include, for example, expanded utilization of Central Institutional Review Boards (CIRBs) for multi-site studies. This strategy has the potential to minimize administrative burdens associated with clinical trials. The Endocrine Society therefore recommends that the Committee encourage the Office for Human Research Protections to issue guidance on the implications of using CIRBs and provide assurance that users of CIRBs are protected from additional liability.¹ Also, the Committee should encourage federal agencies to standardize forms between different federal research agencies and across funding mechanisms as described in the recent National Science Board report².

Another critical issue that strongly affect the translation of biomedical research to therapeutic inventions is the rigor with which biomedical research is undertaken. Unless the basic research that informs drug development is sufficiently holistic, rigorous and thus replicable, downstream R&D could be based on fundamentally flawed information, thus wasting resources and potentially injuring clinical research volunteers. The NIH is proactively

¹ [Endocrine Society Position Statement on Central IRBs](#). Accessed May 20, 2014

² <http://www.nsf.gov/pubs/2014/nsb1418/nsb1418.pdf>. Accessed May 27, 2014



addressing this issue through a number of ongoing initiatives³, and we encourage the Committee to support these efforts and work with the NIH to identify ways to enhance the quality of research outcomes and reporting of research methods. Specifically, we recommend that the Committee identify incentives for researchers and institutions that encourage independent validation of basic science studies with potential clinical application.

In addition to the reproducibility of basic research, the generalization of data requires that all stages of the biomedical research cycle include a consideration of sex differences in research subjects where appropriate. A significant component of the rigor and completeness in research is the investigation of sex specific effects. Despite decades of awareness of the issue, women are still inadequately represented in many clinical trials. Additionally, sex differences are still not routinely considered as a critical variable in basic biological studies. This critical inconsistency in the biomedical research pipeline can have serious consequences. For example, of the 10 drugs that were withdrawn from January 1, 1997 through 2001, 8 posed greater health risks for women⁴.

The NIH and FDA are working to address this important issue; for example, the FDA is required to develop an Action Plan that includes an “analysis of the extent to which demographic subgroups, including sex, age, racial, and ethnic subgroups, are represented in clinical studies to support applications for approved or licensed new molecular entities, biological products, and devices⁵. Additionally, the NIH is developing new policies to ensure that preclinical research includes consideration of sex differences in cell and animal models⁶. The Endocrine Society therefore recommends that the Committee ensure that the NIH and FDA adopt policies that support the consideration of sex as a biological variable and that these policies are efficiently implemented and widely adopted without introducing excessive financial and administrative burdens on preclinical researchers.

We would like to further emphasize that education and mentorship are extremely important as the frontiers of biomedical knowledge progress towards more complicated and interdisciplinary techniques, analysis, and interpretation. It is, therefore, necessary that there are investments in the current generation of scientists, in the forms of steady funding mechanisms, to ensure our scientific future. Trainees and students should be engaged at all stages of education to promote a greater understanding of the biomedical research cycle and the role of federal research investments in the development of cures and treatments for diseases. Mentors and trainees should also be encouraged to explore opportunities to collaborate with partners in the private sector.

³ [NIH Plans to Enhance Research Reproducibility](#). Accessed May 20, 2014

⁴ <http://www.gao.gov/new.items/d01286r.pdf> Accessed May 20, 2014

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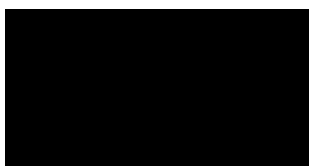
<http://www.fda.gov/downloads/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdact/significantamendmentstotheact/fdasia/ucm365544.pdf>. Accessed May 20, 2014

⁶ [Policy: NIH to balance sex in cell and animal studies](#). Accessed May 20, 2014



Finally, while we appreciate the need to accelerate the process from basic discoveries through delivery of new therapies to the extent possible, research is by nature a labor- and time-intensive process that relies on validated discoveries and consistent replication to build an expanding foundation of knowledge for complicated biological systems. Reliable and protected sources of federal research funding will allow researchers to effectively and responsibly continue to make new discoveries and to explore innovative research areas, especially for diseases such as obesity, diabetes, and osteoporosis. The increasing global burden of these chronic disease make regular investment in human health an urgent priority.

Thank you for considering the Endocrine Society's comments and for your strong and continuing support of biomedical research. We hope that our recommendations are helpful as you consider legislative solutions and regulatory barriers to the efficient progress of biomedical science. If we can be of any further assistance in your efforts, please do not hesitate to contact Joseph Laakso, Associate Director of Science Policy at jlakso@endocrine.org.



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President,
Endocrine Society



JDRF appreciates the opportunity provided by Chairman Upton, Representative DeGette, and the Committee on Energy and Commerce to share comments on biomedical innovation and ways that conditions in the United States can be optimized to accelerate new therapies in the 21st Century. JDRF applauds the Committee for focusing on how Congress can ensure policies that foster the discovery, development, and delivery of promising new treatments to patients.

ABOUT JDRF AND TYPE 1 DIABETES

JDRF, formerly known as the Juvenile Diabetes Research Foundation, is the leading global organization funding type 1 diabetes (T1D) research. JDRF's goal is to progressively remove the impact of T1D from people's lives until we achieve a world without T1D. T1D is a chronic condition where the body is unable to produce insulin, a hormone that regulates blood glucose levels, which often over time results in costly and debilitating long-term complications such as kidney failure, nerve damage, cardiovascular disease, blindness and amputations. As blood glucose levels can move quickly from healthy to dangerous levels, proper management requires monitoring 24 hours a day, 7 days a week.

JDRF has \$568 million invested currently in T1D research, \$106 million of which was committed in 2013. JDRF's research portfolio is strategically designed to fund research programs across the drug delivery pipeline with the recognition that no single discovery is likely to result in T1D being cured or prevented. As such, JDRF invests in a series of research programs across a variety of therapeutic approaches, including novel treatments to help prevent onset and slow progression of the disease, control the symptoms of T1D more effectively, remove or lessen the burdens of living with T1D, and lower the risks of long-term complications from T1D.

Given the growing economic and personal burden of the disease, diabetes research has never been more important than it is today. Currently, 25.8 million people in the United States are affected by diabetes of some form. Management of the disease and its complications cost our nation \$245 billion in medical and economic expenses in 2012ⁱ, a figure expected to more than double to \$512 billion by 2020. These expenses have a significant impact on Medicare, which in 2012 attributed \$104 billion of its costs to diabetes.ⁱⁱ A recent study projects these costs to increase to \$226 billion by 2020.ⁱⁱⁱ In addition to the rising costs, incidence of the disease is also rising. The prevalence of T1D in Americans younger than age 20 rose by 23 percent between 2001 and 2009^{iv}, which, if unabated, means the prevalence of the disease would double for every future generation. The same research found that type 2 diabetes has increased 21% among American youth aged 10-19 in the same period.

COMMENTS ON THE DISCOVERY, DEVELOPMENT, AND DELIVERY CYCLE

JDRF agrees that the discovery, development, and delivery process is a cycle – outcomes in the delivery phase can drive action towards discovery and development of next generation therapies. We applaud the Committee for recognizing that government agencies, the private sector, and nonprofit institutions each play critical roles in this cycle. As the Committee moves forward in its 21st Century Cures initiative, we would highlight the following issues as important areas of focus:

Continued Federal Investments in Discovery Research, Especially in Areas of Unmet Need

It's critical for the U.S. Congress to continue its strong investment in discovery science. It is particularly important for the federal government to invest in areas of unmet need.

Type 1 diabetes is an area of large unmet need, and JDRF is grateful for the leadership of this Committee and Congress' strong bipartisan support of the Special Diabetes Program, which is an essential component of the federal government's commitment to T1D research. The combination of federal diabetes research funding and JDRF's private investment represents one of the world's most effective public-private partnerships focused on curing a disease. This collaborative partnership, along with academia and the private sector, has made important discoveries in promising lines of research including islet cell encapsulation, beta cell restoration, smart insulin, T1D prevention, and kidney and eye-disease prevention and treatment. These areas of study require significant resources, and with the continued collaboration of public and private research programs, the most promising lines of study to cure, treat, and prevent T1D can be advanced, making a difference in the lives of those with T1D and reducing healthcare costs.

Innovative Approaches to Provide Incentives for Translation in Areas of Unmet Need

As a patient led organization, JDRF seeks to ensure promising discoveries are translated into therapies for the people who need them most. Today, many nonprofit charitable organizations such as JDRF use donor dollars to co-fund testing of promising therapies in Phase I & II studies to help prevent them from being abandoned in the Valley of Death. JDRF encourages the Committee to focus on ensuring there are adequate incentives for translation in areas of unmet need, where a disease may not be small enough to be considered an 'orphan disease' but is not large enough to produce a blockbuster product.

NIH funds can also play a role in areas of unmet need where commercial incentives are minimal. For example, NIH, using funds from the Special Diabetes Program, is currently funding a clinical trial using a generic drug that has promise for preventing kidney failure among those with T1D. Because the drug is in generic form, there is limited commercial incentive to test this compound for this purpose, despite the great health and fiscal costs from kidney disease. Diabetes is currently the leading cause of kidney failure, which costs Medicare \$29 billion a year. The large-scale study will examine the potential benefit of allopurinol, a nearly 50-year old drug currently used to treat gout. JDRF funded an earlier pilot study of allopurinol that has laid the foundation for this larger study, funded by NIH through the Special Diabetes Program.

Should this study demonstrate allopurinol's effectiveness in slowing or stopping the loss of kidney function in people with T1D, it could be a major step toward preventing or delaying kidney failure in those who show early signs of kidney damage. Given the availability, low cost, and safety of the drug, a tangible treatment for people with T1D could follow in the study's footsteps.

Mechanisms to Encourage Translation of Knowledge Gained from Discovery Research into Practical Tools for Therapy Development

For years, scientists funded by NIH and JDRF have been studying the progression of T1D before symptoms manifest themselves in order to explore possibilities of prevention therapies. In 2013, breakthrough results from a decade long study were published in *The Journal of the American Medical Association*, which found that children who had at least two autoantibody markers invariably progress to develop symptomatic T1D (i.e., requiring insulin). This finding has great implications for design of clinical trials and the evaluation of potential risks and benefits of potential prevention therapies. To ensure these findings are utilized for therapy development, JDRF is actively working with researchers and officials from NIH and FDA to evaluate the implications for these results and how they can be utilized in translational development. JDRF encourages the committee to consider whether there are mechanisms that could be created or expanded that would encourage similar collaborative efforts to translate knowledge gained from discovery research into tools for therapy development.

Additional Clarity in Regulatory Processes to Spur Translation of Academic Ideas into Commercial Products

Timely and consistent FDA guidance is critical to create a predictable and informed product development environment, particularly in the area of evolving science. JDRF applauds recent FDA efforts to work with stakeholders to ensure adequate guidance and interactive review in the area of artificial pancreas systems, and believe this could be a model for other areas. Because such proactive engagement on behalf of the agency requires significant resources, JDRF would encourage the Committee to ensure the agency is funded at a level enabling it to conduct 21st century regulatory science.

Artificial pancreas (AP) systems will be a revolutionary advance in diabetes care and are promising near-term opportunity to improve life for people with T1D. The artificial pancreas is one of the FDA's Critical Path initiatives, and the FDA has been engaging with JDRF and other stakeholders since 2005. Utilizing continuous glucose monitoring (CGM) technology with insulin pumps and sophisticated computer algorithms, AP systems will react to changing glucose levels to provide the right amount of insulin at the right time, mimicking the pancreas of someone without diabetes. Such AP systems will result in much tighter control, lowering the risk of health complications later in life and reducing low blood sugar emergencies.

The NIH, the FDA, and JDRF have identified an innovative continuum of AP systems, progressively advancing technology to an end goal of a completely closed-loop system. The first generation is designed to suspend insulin delivery upon reaching low blood glucose thresholds, reducing incidence of the immediate dangers associated with hypoglycemia. Future generations of AP technology will progressively evolve to keep blood glucose levels within a certain range by turning insulin delivery on and off in response to high or low blood sugar. These generations lead to a final phase of development where devices will automatically keep blood sugars at specific levels, with added capability to deliver doses of key pancreatic hormones, such as glucagon or amylin, which also influence glucose levels.

JDRF began funding artificial pancreas research in 2006, and NIH soon joined in. By 2010, research in in-patient hospital settings was showing great promise, but the regulatory pathway to translate these academic feasibility studies to commercial development was not clear. As a result, JDRF convened a clinical recommendations panel and proposed draft guidance to the FDA for consideration. After an

active debate and discussion over draft versions, the FDA issued final guidance in November 2012, which laid out clear and reasonable guidelines.

This FDA guidance has helped catalyze research and development of artificial pancreas systems. While first generation AP system – low glucose suspend technology – were delayed in the United States given the previously unclear pathway, this device has since been approved by the FDA and is now on the market and available to patients. Moving forward, we are hopeful that next generations of AP systems will advance without delay. Already, multiple versions of next generation AP systems are in outpatient clinical trials supported by JDRF and NIH and the results thus far are very encouraging. Participants in the outpatient trials have enjoyed typical daily life activities — going for walks, out to eat in restaurants, and to work — with these experimental technologies that automatically controlled their blood sugar, giving a glimpse into what the future holds for T1D management. Companies are working on proprietary versions of these systems, utilizing the regulatory pathway in the guidance.

As outpatient clinical trials continue, JDRF looks to continue its productive partnership with the NIH, FDA, and diabetes clinical groups to move AP technology forward without delay.

Facilitating Patient Access to Innovative Therapies

JDRF also encourages the Committee to focus on ensuring health care access for patients to innovative therapies. Lack of affordable health care coverage and reimbursement can be as much an impediment to future medical research discoveries as they are an impediment to improved health, providing disincentives to future private sector investment into new therapies and improvements to currently approved therapies.

Continuous Glucose Monitoring (CGM) technology, one component of previously noted artificial pancreas systems, are an example of how sometimes government funded health care lags behind the private sector, to the detriment of patients and incentives for innovation. There is extensive clinical evidence of the benefits of CGM in improving glucose control and reducing rates of severe hypoglycemia, both from a JDRF-funded trial, whose results were published in the *New England Journal of Medicine*^v and *Diabetes Care*^{vi}, and other studies evaluated by the Agency for Healthcare Research and Quality.^{vii} Based on this clinical evidence, diabetes clinical guidelines by all leading diabetes professional societies recommend use of a CGM, including the American Association of Clinical Endocrinologists,^{viii} the American Diabetes Association,^{ix} and The Endocrine Society,^x and today, approximately 95 percent of all private insurers cover CGM technology.

However, Medicare does not cover CGM devices, leaving vulnerable seniors with diabetes, who already have disproportionately high rates of hospitalization and emergency room use. We would encourage the Committee to consider ways to ensure that publicly funded health care programs do not lag behind private sector plans in providing patient access to innovative technologies. Medicare coverage of this technology would not only serve to assist more people with T1D to fine-tune their management using this breakthrough technology, but would also encourage ongoing investment and exploration into artificial pancreas technologies.

CONCLUSION

JDRF appreciates the opportunity to share thoughts on important factors to accelerating medical research progress in the United States. JDRF is grateful for the strong partnership with Congress, the National Institutes of Health, and the Food and Drug Administration to advance all facets of discovery, development, and delivery of therapies until we create a world without type 1 diabetes.

ⁱ American Diabetes Association. (2013). Economic Costs of Diabetes in the U.S. in 2012. *Diabetes Care*, 36(4), 1033-1046. doi: dc12-2625.

ⁱⁱ Ibid.

ⁱⁱⁱ Shapiro, R. and Pham, N. (2013). *Diabetes Research and the Public Good: Federal Support for Research on Type 1 Diabetes*. Washington: Sonecon.

^{iv} Mayer-Davis, E., Dabelea, D., Talton, J.W., Hamman, R.F., Divers, J., Badaru, A., and Saydah, S.H. for the SEARCH for Diabetes in Youth Study Group. (2012, June). *Increase in prevalence of type 1 diabetes from the SEARCH for Diabetes in Youth Study: 2001 to 2009*. Presented at the American Diabetes Association 72nd Scientific Sessions, Philadelphia, PA.

^v JDRF CGM Study Group, *N Engl J Med* 2008 359:1464-1476

^{vi} JDRF CGM Study Group, *Diabetes Care* 32:2047-2049, 2009

^{vii} Golden et. Al. Comparative Effectiveness Review No. 57. AHRQ Publication No. 12-EHC036-EF. July 2012

^{viii} *Endocrine Practice* Vol. 16 No. 5 September/October 2010

^{ix} *Diabetes Care*, Vol. 36, Supplement 1, January 2013, p S17

^x *J Clin Endocrinol Metab*, October, 2012, 96 (10): 2968-2979



Submitted in Electronic Form to cures@house.gov

June 3, 2014

Chairman Fred Upton
Rep. Diana DeGette
House Energy and Commerce Committee
2125 Rayburn House Office Building
Washington, D.C. 20515

Re: 21st Century Cures Initiative

Momenta Pharmaceuticals, Inc. (“Momenta”) is pleased to provide these comments to the House Energy and Commerce Committee’s 21st Century Cures Initiative. Momenta is a leader in the analysis, characterization, and design of complex pharmaceutical products. Our scientific foundation is a set of tools and methods that enable one to develop a deep understanding of the links between a compound’s chemical structure, its manufacturing process and its biological function. These innovative tools enable us to develop complex generics and biosimilars as well as facilitate the discovery of novel medicines. We believe that by applying our innovative technology to our discovery and development programs, we have the potential to create a robust pipeline of innovative generic and novel medicines.

Innovation is the key to the advancement required for safe and effective biosimilars. Innovation is also essential to overcoming obstacles to the discovery, development and delivery of lifesaving medicines. What can be lost in the discussion, however, is the essential role that disruptive biosimilar innovation can and does play in making life saving treatments available and affordable to all Americans. A workable biosimilar regulatory pathway is essential to this process and in turn to the timely development of novel and biosimilar biologics. Restrictions on this pathway will deter innovation, promote the status quo, and make it difficult to raise capital and to invest in quality enhancing biosimilar innovation.

Thirty years ago this Committee, Congress and the President enacted and signed into law the Hatch-Waxman statute recognizing, that after patents expire, competition could make established medicines more affordable and accessible. Perhaps an even more powerful impact of the Hatch-Waxman law, over its thirty year period, is the innovation driving effect it had and has on the development of breakthrough medicines. We became the world leaders in biotech over the past 30 years in part due to the disruptive innovation of the Hatch-Waxman law.

Hatch-Waxman promoted innovation in several ways. First, it creates savings for payors resulting from generic competition (over \$1 trillion in the last ten years)¹ – *savings that*

¹ Over the 10-year period 2003 through 2012, generic drug use has generated more than \$1.2 trillion in savings to the health care system.

http://www.gphaonline.org/media/cms/2013_Savings_Study_12.19.2013_FINAL.pdf

importantly are plowed back into paying for new patented breakthrough medicines by creating critical “headroom” in payor budgets for new cures. Today generic medicines account for nearly 85% of prescriptions in the United States, and as a result they make life saving medicines (both new and established) accessible and affordable.

Generic competition also created a huge incentive in the 1980s and 1990s for pharmaceutical innovators to steer investment into breakthrough biotechnology innovation leading to both small molecule and biologic therapies that were unimaginable in the 1980s – e.g., monoclonal antibodies for treating many cancers and autoimmune disorders, targeted small molecule therapeutics that selectively target disease. Because of the expectation of generic competition, companies had a reason *not* to invest in so called “me too” products that did not address unmet medical needs because of limited profit opportunity, and instead to invent new cures. This symbiotic relationship has proved to be one of the greatest innovation driving success stories flowing from Hatch-Waxman and helps explain why we lead the world in biopharmaceutical research. *Restrictions on the use of the biosimilar regulatory pathway could reverse our global competitive advantage by not applying the same innovation incentives to novel biologic research and development as Hatch-Waxman did for novel medicines.*²

The opportunity to develop biosimilars also led biologics companies, like Momenta, to invest in research to better understanding biologics - products that were once thought to be too complex for generic-like development. Congress, wisely recognized this, and adopted a biosimilar pathway for the Food and Drug Administration (FDA) in 2010 in the Biologics Price Competition and Innovation Act (BPCIA) that was designed to spur innovation of biosimilar technology as well as novel therapeutics. A goal was to spur innovation for biologics as Hatch-Waxman did for drugs. Congress did not amend the Hatch Waxman law because of the recognition that substantial innovation would be needed to thoroughly understand the science of biologics for biosimilars to be a success. Congress instead of authorizing “generic biologics,” provided for two kinds of biosimilar approvals: biosimilars that are highly similar to the reference product; and interchangeable biologics that have been shown to the FDA to be capable of substitution at the pharmacy without the intervention of a physician. Some at the time did not believe that innovation could make the interchangeable pathway possible. Momenta, and others argued at that time, and Congress decided, that the law should not bar innovation of biosimilar and interchangeable biologic science. The Biologics Price Competition and Innovation Act allowed for the FDA to consider the best science to demonstrate biosimilarity and interchangeability, and created an incentive for the capital markets to finance investment in this important new field. Today we are optimistic that the investments and the innovation that has been spurred to date and that continues will lead to safer biologics (both originator and biosimilar) as a result of the innovative science that allows us to increasingly understand the

² Notably, while a biosimilar pathway was adopted in 2006 in Europe, it did not drive innovation in the same manner as the BPCIA. It was not until the enactment of the biosimilar pathway in the United States, and the opportunity to develop interchangeable biologics created, that significant scientific innovation began that relies on state of the art science to demonstrate “biosimilarity” and “interchangeability.” The early products in Europe were not developed to be interchangeable, and relied primarily on clinical trials to demonstrate biosimilarity. As noted below, at pages 12-14, the science of comparison requires more careful analytical studies, and the FDA is driving the industry to innovate and bring the highest quality products to market. Europe, in response, is adopting guidance that is now increasingly aligning with the FDA because of our global scientific leadership.

composition of a biologic, measure its characteristics, and control with increasingly greater precision biologics manufacturing processes.

Today, these advances are making it possible and real to expect that both biosimilar and interchangeable biologic competition will be arriving in the market in the next few years as patents expire on the first generation of biotechnology breakthrough cures. *Time is of the essence because by 2016, 8 of the 10 highest selling originator products will be biologics (products that are 22 times more expensive than small molecule drugs).*³ The resulting impact of innovation driven by Hatch-Waxman, and the number of small molecule products with patent expirations are declining as a result. *If biosimilars and interchangeable products are restricted and launches are impaired, potentially \$250 billion in savings, savings that make life savings treatments affordable and accessible may not come to pass, and biosimilar launches that drive innovation of new cures could be delayed or prevented.*⁴

Today, originator companies are continuing to fight these pro-competitive innovation incentives for biosimilars and interchangeable biologics. They are seeking to promote policies that restrict competition, and create barriers to entry – because barriers to entry protect profit on established, older products and relieve them of the need to invest in the development and innovation of new cures. They are seeking to restrict the entry of biosimilars and interchangeable products by asserting, without scientific evidence, that these products will not perform as intended and approved, that they have suspect “safety profiles”, and that they should therefore have different names. They also have launched a nationwide campaign to undo federal legislation at the state level to interfere with substitution of interchangeable biologics, which by definition are biosimilars that are determined by the FDA to be substitutable at the pharmacy without the intervention of a physician. While intentionally not being transparent about their motives, the history of opposition to the biosimilar pathway by these opponents makes the real motive clear – to restrict competition and impede innovation so that they do not have to invest in the next generation of new cures to be profitable.

We urge the Committee as part of its 21st Century Cures initiative to:

- support the biosimilar pathway;
- oppose restrictions on biosimilar innovation and investment;

³ Testimony of Bruce Leicher, Momenta Pharmaceuticals, at Workshop at 9 (Feb. 4, 2014). http://www.ftc.gov/system/files/documents/public_events/Follow-On%20Biologics%20Workshop%3A%20Impact%20of%20Recent%20Legislative%20and%20Regulatory%20Naming%20Proposals%20on%20Competition/leicher.pdf ; A copy of the Powerpoint Presentation is attached to this Letter.

⁴ Testimony of Steve Miller, MD, Express Scripts at Workshop at 7 (Feb. 4, 2014) http://www.ftc.gov/system/files/documents/public_events/Follow-On%20Biologics%20Workshop%3A%20Impact%20of%20Recent%20Legislative%20and%20Regulatory%20Naming%20Proposals%20on%20Competition/miller.pdf

- encourage the FDA to adopt a naming policy that does not interfere with competition by requiring unique and confusing nonproprietary names;
- oppose a state substitution legislation that adopts restrictive notification laws at the State level that, in effect, write interchangeable biologics out of the BPCIA when the law expression contemplates substitution at the pharmacy -- particularly when innovative, pro-competitive methods to inform physicians already exist ; and
- promote our continued global leadership in biopharmaceutical innovation in the 21st Century.

DISCUSSION

Momenta participated at the February 4, 2014 Workshop⁵ (the “Workshop”) at the FTC that examined anticompetitive restrictions associated with the naming of biosimilars and the substitution of interchangeable biologics at the pharmacy. Momenta believes that:

- Biosimilar and interchangeable biologic policy should be driven and measured by how it:
 - Promotes innovation and attracts investment in delivering safe, effective and affordable biologics
 - Addresses patient needs (including access) and patient safety
 - Avoids using the least innovative and most anti-competitive solutions to achieve these important objectives.
- The opposition to biosimilar and interchangeable biologic competition have much to lose financially when patents and exclusivity expire for a brand product
 - Financial loss and risk is what really motivates the proposals for state substitution restrictions and naming barriers to biosimilar and interchangeable biologic competition
 - State substitution restrictions and differential naming will create barriers to investment in the innovation necessary to provide access to safe, effective and affordable biologics
 - The loss of competition will decrease the incentive for brand companies to innovate the next generation of new cures if patent or exclusivity profits continue after expiration or loss of exclusivity
- The Federal policy should therefore encourage the FDA or HHS to adopt a policy stating that:

⁵ See Follow-On Biologics Workshop: Impact of Recent Legislative and Regulatory Naming Proposals on Competition (Feb 4, 2014). <http://www.ftc.gov/news-events/events-calendar/2014/02/follow-biologics-workshop-impact-recent-legislative-regulatory>

- State substitution restrictions are an unlawful conflict with Section 351(i) of the BPCIA; and
- The benefits of innovation already underway from ePrescribing, the Sentinel Initiative and other programs, and the confusion that naming differences would cause, mean that biosimilar and interchangeable biologics should share the same non-proprietary name

At the FTC Follow-On Biologics Roundtable in 2008, Momenta provided evidence to demonstrate how the opportunity to develop generic biologics (now referred to as interchangeable biologics) would spur innovation and benefit consumers.⁶ The inclusion of an interchangeable biologics designation under Section 351(k)(4) along with explicit authority for the FDA to consider innovative science and exercise discretion to waive clinical and other development requirements has now made it possible to reduce development costs and finance development of affordable biosimilars. Interchangeability is competitively critical because under 351(i):

...the [Interchangeable Biologic] may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.

The BPCIA also explicitly recognizes that an interchangeable biologic is not a “new active ingredient” as a result of this additional approval requirement, while a non-interchangeable biosimilar is considered a “new active ingredient.”⁷ This is why an interchangeable biologic is substitutable and switchable. Accordingly, interchangeable biologics should not be subject to additional requirements that would trigger physician intervention (requirements that were contemplated for non-interchangeable biosimilars such as physician notice and pre-authorization).

Thoroughly characterizing and understanding biologics and engineering the process controls to assure biosimilarity and interchangeability is no longer “impossible,” but involves difficult and costly innovation. Companies like Momenta have relied on the opportunity created by the Section 351(k) pathway in making the decision to invest. This kind of innovation enhances the level of understanding of all biologics, and it makes affordable biologics possible

⁶ See Comments of Momenta Pharmaceutical, Inc., FTC Roundtable on Follow-On Biologics, December 22, 2008. <http://www.ftc.gov/news-events/events-calendar/2008/11/emerging-health-care-competition-and-consumer-issues> .

⁷ Section 351(n) of the BPCIA, for example, only applies the “new active ingredient” special studies requirement under Section 505B to non-interchangeable biosimilar biologic products, as follows:

- (1) Non-Interchangeable Biosimilar Biologic Product. -- A biological product that is biosimilar to a reference product under section 351...that the Secretary *has not* determined to meet the standards described in subsection (k)(4) of such section for interchangeability with the reference product, *shall be considered to have a new active ingredient* under this section.
- (2) Interchangeable Biosimilar Biologic Product.—A biologic product that is interchangeable with a reference product under section 351...*shall not be considered to have new active ingredient* under this section.

through a reduction in clinical trial requirements and related development, commercialization and marketing costs. Consumers will benefit from the potential for improved access to both higher quality and more affordable products. If the opportunity for substitution at the pharmacy is impaired by state law restrictions, or by naming requirements, these barriers would then have to be overcome by the use of branding and marketing. This, in turn, would necessitate scientifically unwarranted, expensive clinical trials to generate marketing data to arm and employ a sales force. Collectively, the incentive to invest and innovate interchangeable biologics as envisioned by the BPCIA would be seriously eroded by these barriers to entry.

Our comments focus on three key areas:

- **Historical Context:** There is a substantial history of opposition to biosimilars, and in particular to interchangeable biologics. These efforts are to be expected given the serious competitive alternative created by these products to high priced biologics -- products that are at the peak of their annual revenues when patent rights expire and, when first developed, did not envision the innovative science that would make biosimilar and interchangeable biologic competition a reality.
- **State Substitution Restrictions:** The battle to prevent substitution of generic biologics was lost at the federal level with the enactment of the interchangeability designation under Section 351(k). Historical opposition has shifted to the States to implement restrictions on substitution. Recently, this effort to restrict interchangeable biologic competition has also been supported by some biosimilar companies seeking to protect their future “marketed” biosimilar sales from interchangeable competition. Notably, many of these same companies also develop and market “innovator” biologics that they are also trying to protect from competition. In addition, a key secondary objective of these state substitution laws is to label interchangeable biologics as “different” much in the same way that biosimilars are “claimed” to be different to deter substitution, in order to influence prescribers and make marketing and sales activities a barrier to interchangeable biologic market entry. If this secondary objective succeeds, the costs of unnecessary clinical trials would render interchangeable biologics significantly less competitive or non-competitive due to their innovation costs.
- **Naming Impediments:** Biosimilar naming is an additional tactic being employed by opponents to biosimilars in their advocacy at the FDA and global naming authorities. Their objective is to make biosimilars and interchangeable biologics look different to physicians than reference products and erect barriers to market entry. Differences are used to raise fears and disparage biosimilars and interchangeable biologics. Different names are used to suggest they may not have been demonstrated to be as safe and effective as the reference brand product, when in fact the FDA must determine they have no meaningful clinical differences to the reference product, and for interchangeable biologics, are substitutable and switchable without the need for physician intervention. A different name also means that every time a physician is asked to write a prescription for a biosimilar, a message of difference is delivered through its name – a message that would be unsupported by data and could not be made in promotional material after an FDA finding of biosimilarity or interchangeability. The argument that post-marketing pharmacovigilance requires biosimilars to have different names is misplaced. The

pharmacovigilance concerns that have been raised exist for all products and are best solved by the use of innovative tools, and by a pro-competitive approach for all products. Every product needs to be tracked by lot number and manufacturer to capture quality defects, not just biosimilars. This information is already stored by pharmacists and is available to physicians nationwide electronically or by phone for pharmacovigilance needs. At the same time, differential naming also creates a risk of balkanization of rare safety events by suggesting reference product and biosimilar adverse events may not be related and could interfere with detection of rare events, rather than enhance it.

As the facts and motives are sifted, it becomes increasingly clear that the state substitution restrictions and naming proposals are the current wave of tactics being employed to deter or prevent effective innovative competition from more affordable biosimilar and interchangeable biologic products.

1. Historical lobbying and regulatory advocacy demonstrates that the real motive for state substitution restrictions and differential naming is to entrench barriers to competition into the legal and regulatory pathway and to protect branded product market share from innovation of safe and affordable biosimilars and interchangeable biologics.

There is a well-documented history of lobbying efforts to enact laws and regulations to restrict competition.⁸ In 2003, the anti-competitive message was most direct. E.g., There must not be biosimilars because generic biologics are impossible, biologics can only be defined by a manufacturing process, not by the product, and biologics are impossible to characterize and replicate. These arguments continue to exist and underlie the current anti-competitive proposals. For example, based on these arguments, the Biotechnology Industry Organization (BIO) filed a Citizen Petition with

A Long Established Campaign Against Biosimilar Innovation and Competition		
Tactic	Message	Barriers to Competition
BIO CP - 2003	<ul style="list-style-type: none"> Generic Biologics are Impossible 	<ul style="list-style-type: none"> Prevent Regulatory Approval Prevent/Deter Legislative pathway
Oppose Biosimilar Pathway – 2007-2010	<ul style="list-style-type: none"> Biosimilars are unsafe even if possible Interchangeable biologics are impossible/different 	<ul style="list-style-type: none"> Prevent/Deter pathway Incorporate legislative features that prevent/deter use of the pathway <ul style="list-style-type: none"> Mandatory Clinical Trials Complex IP exchange
Influence FDA Guidance - 2011	<ul style="list-style-type: none"> Same messages 	<ul style="list-style-type: none"> Emphasize differences (Eg. Naming) Mandate Unnecessary Clinical trials Freeze scientific standards for similarity and interchangeability
Abbvie CP	<ul style="list-style-type: none"> Same messages 	<ul style="list-style-type: none"> Delay Biosimilars for 10 years
Naming Campaign JnJ Citizen Petition	<ul style="list-style-type: none"> Biosimilars are different and raise safety concerns 	<ul style="list-style-type: none"> Amplifies anti-biosimilar commercial campaign with providers, payors, patients and regulators
Restricted Access to Reference Products	<ul style="list-style-type: none"> Biosimilar companies are irresponsible 	<ul style="list-style-type: none"> Prevents/Delays initiation of development

⁸ W. Nicholson Price II, Academic Fellow, Petrie-Flom Center for Health Law Policy, Biotechnology and Bioethics, Harvard Law School, recently did a study of pharmaceutical CMC innovation and found that regulatory barriers and calcification may be the principal cause of the absence of innovation in quality by design in pharmaceutical manufacturing; the area where biosimilar and interchangeable biologics companies are most innovative. Price, Making Do in Making Drugs: Innovation Policy and Pharmaceutical Manufacturing (2013); <http://ssrn.com/abstract=2311682> . It is not surprising that industry seeks to enact into law and regulation limits on innovation to impede competition, particularly in the biosimilars field.

the FDA seeking to ensure that the FDA not approve any generic biologics or biosimilars.⁹ In the 2003 CP, BIO cited a 1999 FDA Guidance for Industry: Applications Covered by Section 505(b)(2) and challenged its “suggestion” of the “possibility of follow-on approvals” under an abbreviated regulatory pathway.¹⁰ As a basis for 2003 CP, it stated:

Current science demonstrates that there can be no abbreviated approach to the approval of therapeutic proteins, whether licensed as biological products or approved as new drugs. There are significant differences between therapeutic protein products and “chemical drugs” – in size, complexity, and heterogeneity – and each manufacturer must provide its own full complement of original data....

Patient Safety is the primary concern when discussing proposals to reduce product testing. BIO is, in particular, concerned that significant risks to patient safety would arise if biologically derived products were to be approved based on less than a full complement of original data concerning each manufacturer’s product. In addition, BIO is concerned that any safety problems that could develop as a result of such approvals could undermine the confidence of physicians and patients in biologically derived products.

These two key advocacy messages have not changed in over 10 years, but rather have been re-packaged and reissued in different forms as innovative science demonstrates their obsolescence. Scientific innovation, in our view, no longer prevents biosimilar and interchangeable biologic competition. We must not tolerate the enactment of state laws and advocating rules and policies whose purpose is to achieve the same anti-competitive objective. These messages assume that (A) innovation in characterizing proteins is impossible, and (B) the product will always be defined solely by the process. They are designed solely to raise fears and concerns. Ultimately, the 2003 CP failed in that the FDA approved an application for Omnitrope (somatropin [rDNA origin] for injection) under Section 505(b)(2) based on an abbreviated application.¹¹

In the years following approval of Omnitrope, the legislative campaign to authorize the FDA to approve follow-on biologics began in earnest, leading to a number of proposed bills in the House and the Senate. The various bills ranged in diversity from bills authorizing approval of generic biologics, to bills authorizing only the approval of biosimilars based on mandatory clinical trials providing originator-like data, to the final Senate HELP draft enacted as the BPCIA which contemplates approval of biosimilars as well as interchangeable biologics. Throughout the legislative debate, these same messages were asserted by opponents to biosimilar competition while in parallel innovation continued by potential new entrants in this market.

Despite the assertion that biologics could not be thoroughly characterized, understood and replicated, Congress had the wisdom not to legislate a ceiling on innovation and provided the FDA with the scientific discretion to vary the development requirements for applicants based on

⁹ BIO Citizen Petition: Follow-On Therapeutic Proteins (April 23, 2003) , Docket No. 03P-0176 (the” 2003 CP”).

¹⁰ 2003 CP at 2.

¹¹ Letter from the Director, Center for Drug Evaluation and Research to Petitioners (May 30, 2006); Docket Nos. 2004P-0231/CP1 and SUP1, 2003P-0176/CP1 and EMC1; and 2004N-0355.

an applicant's ability to demonstrate its understanding and replication of the reference product.¹² This created a powerful market incentive for companies like Momenta to invest in innovative technology to develop biosimilars and created a reward (i.e., abbreviated development) for this innovation. In addition, Congress enacted a separate designation for interchangeable products, to create an incentive to invest in development if interchangeable biologics that could be substituted and switched at the pharmacy without the need for physician intervention.¹³

The enactment of the BPCIA was a breakthrough moment, and one that is leading to pro-competitive, disruptive innovation. Yet undeterred, the opponents of biosimilars and interchangeable biologics continued to make the same arguments to the FDA during its development of guidance documents. In comments filed in 2010 before the FDA, for example, BIO's major message appeared designed to make the pathway too difficult and expensive to use by erecting barriers to innovation and competition. The messages included:

- Patients do not have to accept greater risks or uncertainties in using a biosimilar than an innovator's product. Accordingly, approval of biosimilars must be based on the same rigorous standards of safety, purity, and potency applied by FDA for the approval of innovator biotechnology products.
- Clinical trial evidence and data are fundamental for evaluating and demonstrating the safety and effectiveness of a biosimilar, and must be conducted on a product- by-product basis. In particular, immunogenicity testing is necessary to avoid putting patients at risk of adverse effects from immune reactions.
- Biosimilars must be properly evaluated through post-marketing surveillance and post-marketing clinical studies as needed.
- Biosimilars should be assigned a non-proprietary name readily distinguishable from that of the innovator's version of the product. Assigning the same name to a product that are not the same would be confusing and misleading to patients, physicians, and pharmacists, could result in inadvertent substitution of the products, and would make it difficult to quickly trace and address adverse events that may be attributable to either the innovator or biosimilar product.¹⁴

¹² Section 351(k) (2)(A)(ii) provides in relevant part, "The Secretary may determine, in the Secretary's discretion, that an element described in clause (i)(I) [analytical, animal, and clinical studies] is unnecessary in an application submitted under this subsection."

¹³ Sections 351 (i)(3) and 351(k)(2)(B) and 351(k)(4).

¹⁴ The opposition understands the effect labelling of biosimilars with a different name would achieve. For when engaging to oppose state legislation that would require labelling or notice regarding genetically modified food, Jim Greenwood, President and CEO of the Biotechnology Industry Organization (BIO), issued the following statement to the press on November 23, 2013:

Just like 27 million voters in California and Oregon, Washington voters saw how this burdensome and deceptive labeling scheme would have created more state bureaucracy, imposed new costs and burdens on local farmers and businesses, and increased food prices for Washington families.

Food labels should convey valuable and accurate information to consumers. Mandatory initiatives to label all foods containing genetically modified ingredients would only serve to confuse consumers and raise food prices without any additional benefits.

- Prescribers are involved in decisions to switch among biological products.¹⁵

Again, these are messages that assumed by implication that the FDA would not reliably perform its obligations (code words for biosimilars are not really similar or safe and effective), and that clinical trials and originator data were essential for biosimilar approval. Note that interchangeable biologics are not even in the message points because they were still viewed as inconceivable. Thus, opponents argue that a physician must always be involved in the decision to switch among products, and all biosimilars must receive a different name. Immunogenicity is highlighted to amplify the purported patient safety risks, and by implication, an abbreviated approval raises “concerns” as well. In the detailed comments, a whole section is devoted to documenting patient safety and pharmacovigilance “concerns.”¹⁶ Guilt by association with reference product safety concerns seems to be a consistently used argument of choice.

The most frequently cited concerns, however, involve adverse events associated with manufacturing changes to reference products. The comments are silent though about the fact that innovation in the science of understanding the characteristics of biologics may be the more appropriate and innovative solution for addressing these concerns for all biologics and that the type of innovation that would be promoted by the new biosimilar pathway may be the best means to solve the historic problem with biologic quality control associated with product drift, process changes and manufacturing variability. The ability to thoroughly characterize biologics and screen them for defects before delivery to patients would significantly reduce the risk of harm at its source by enabling control of manufacturing more effectively, rather than relying on post-marketing monitoring to catch problems after patients are injured. Because historically reference products relied on “the product is the process”, the incentives to invest in the science that could thoroughly characterize each biologic did not exist and was not believed feasible or possible. Much has been changed by the incentive of the 351(k) pathway to invest and innovate in this capability. Our view then, and today, is that the emphasis of the opposition on these types of arguments is messaging-based. If repeated often enough, it would become dogma and help ensure that if biosimilars, or perhaps even interchangeable biologics were ever approved, that the prevailing view would be they really are different, that they are too difficult to control, and that the risk of their use was not worth the savings. Moreover, the objective was also to require large and extensive clinical requirements that would make their development financially unattractive. These unjustified burdensome requirements would deter or prevent the use of abbreviated approvals that could lead to more affordable products that are just as safe and effective as the reference products. The irony is that the very innovation that would be stifled is directed to preventing the risk opponents are seeking to detect but not necessarily avoid in the first instance.¹⁷ The FDA considered these comments, and considered the prevailing science,

We should ask why physicians, consumers and pharmacists are not also negatively impacted by the stigmatization of substitution restrictions and special naming requirements in the same way that GMO labelling creates disinformation about GMO foods.

¹⁵ Letter from BIO to FDA (December 23, 2010); Docket FDA-2010-N-0477 at page 2.

¹⁶ Id. at pages 17-19

¹⁷ Perhaps the best example of this type of innovation is Momenta’s experience with generic enoxaparin. Enoxaparin is made from heparin that in turn is made in cells like a biologic. It was believed by the brand manufacturer that like a biologic, enoxaparin could only be defined by a manufacturing process and that it was impossible to thoroughly characterize enoxaparin and reverse engineer its manufacturing process to prove sameness.

and adopted draft biosimilar guidance documents in 2011.¹⁸ In its guidance documents the FDA reaffirmed the innovation objectives of the BPCIA and adopted a flexible scientific approach. The approach was discussed by Emily Shacter at the Workshop¹⁹ and is summarized in this slide included in Momenta's presentation.

The FDA Spurs Investment by Promoting Innovation

- Approval Standards are Rigorous**
 - Biosimilars must:
 - Be Highly Similar to the Reference Product
 - Not have clinically meaningful differences
 - Interchangeable Biologics must also:
 - Be expected to perform the same in any given patient
 - Have the same risk associated with switching as the reference product
 - And Most Importantly:
 - Are By Statutory Definition, Substitutable at the Pharmacy without the Intervention of a Physician
- Approach Drives Understanding of what Biologics Are: The Product is not Merely the Process**

Highly Similar Analytical and PK/PD Data Assumes Lower Risk of Clinical Differences

Two approaches to demonstrate biosimilarity

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FDA Response to Citizen Petition of Aventis (sanofi), July 23, 2010.

<http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM220083.pdf>

In the response, the FDA determined it was possible to prove sameness based on thorough characterization. Id. In the course of thoroughly characterizing enoxaparin as a generic, Momenta needed to determine what the active ingredients were as well as the inactive ingredients and develop a thorough understanding of what should and should not be present. A clear benefit of the innovation involved in conducting this research and development was the ability to also use this technology to test blinded samples of heparin for contaminants and this aided the FDA in resolving the safety problem associated with contaminated heparin imported from China. The brand companies that relied on the “product is the process” were not able through ordinary means to detect the contaminant putting patients at risk. See Sasisekharan et. al., Contaminated Heparin Associated with Adverse Clinical Events and Activation of the Contact System, 358 N. Engl. J. Med. 2457-67 (June 5, 2008). The EPREX adverse events that presented themselves with biologics from manufacturing changes might have been detected following a manufacturing change if this kind of technological innovation in analytical science had been conducted to develop a biosimilar to that product. If the opportunity to pursue of abbreviated clinical trials and interchangeability has barriers, it is less likely that this kind of innovation will occur.

¹⁸ 77 FR 8883-8886 (February 15, 2011).

¹⁹ Statement of Emily Shacter at the Workshop.

The Experience with Generic Lovenox is Relevant to the Development of Biosimilars



The FDA also recognized in developing biosimilar guidance that its experience with generic enoxaparin demonstrated that this type of innovation is possible and should be encouraged. The clear import of the FDA’s scientific findings as expressed in its policy was and remains that the science is evolving, and that it is now possible to thoroughly characterize biologics. As a result of the innovation in this developing field, it is increasingly likely that clinical trials, which may be the costliest part of biologic development, can now be

targeted and reduced. The use of analytical science may be the most discriminating means for identifying structural and functional differences. In November 2013, at the Drug Industry Association Meeting, Leah Christl, Ph.D., Associate Director for Therapeutic Biologics on the OND Therapeutic Biologic and Biosimilars Team, provided a key update on the FDA’s activities and on recent biosimilar applicant activity. She shared the following slides to make the point that applicants need to focus on demonstrating biosimilarity, and that clinical trials cannot demonstrate similarity in the first instance but should be targeted to resolving any residual uncertainty that remains after a thorough characterization of the reference brand biologic and the biosimilar development candidate and not to re-proving safety and efficacy:

Dr. Christl emphasized in her November 2013 presentation that one could not use clinical trials to test biosimilarity into a product, because clinical trials are not the most effective means for determining product differences. This was a clear rejection of the anti-innovative policy advocated in comments by opponents to the pathway. More importantly, she made the point that applicants that were taking a clinical trial approach to demonstrating biosimilarity without first proving sufficient biosimilarity through non-clinical means were



Key Concept #7: Comparative Clinical Study

- The nature and scope of the comparative clinical studies will depend on the extent of residual uncertainty about the biosimilarity of the two products **after** conducting structural and functional characterization and, where relevant, animal studies.
- As a scientific matter, a comparative clinical study will be necessary to support a demonstration of biosimilarity if there are **residual uncertainties** about whether there are clinically meaningful differences between the proposed and reference products based on structural and functional characterization, animal testing, human PK and PD data, and clinical immunogenicity assessment.

putting the “Cart Before the Horse” and were advised to do the appropriate non-clinical characterization testing so that biosimilarity was demonstrated and clinical testing could be targeted to resolving uncertainty.



The illustration shows a yellow character with a brain and a question mark on its head, sitting in a red cart pulled by a brown horse. The horse has a question mark above its head. The text below reads: "Lessons learned: Put your horse first..."

Lessons learned: Put your horse first...


She specifically pointed out that applicants should not propose traditional “phase 3” trials, but rather trials designed to demonstrate biosimilarity. This was a clear change in direction from prior approaches in Europe where products had demonstrated biosimilarity using large Phase 3 type trials, and signaled that innovation in the science of characterization was and would guide FDA scientific policy.

The take away point, as Dr. Shacter discussed at the Workshop, is that there has been a substantial advance in the opportunity to thoroughly characterize biologics. The reason opponents to the pathway advocated historically for mandatory large scale safety and efficacy trials is now being exposed. The opposition may have retained credibility in the early years of the debate because there were open questions about where innovation would lead. Now, it is increasingly clear that unless clinical trials are targeted to resolving uncertainty, their primary impact would be to erect a barrier to competition by increasing biosimilar and interchangeable biologic development costs. It would also create a marketplace where clinical data would need to be used to sell a biosimilar or interchangeable biologic further increasing the cost and undermining the value and return on investment in an interchangeability designation.

The history of anti-biosimilar advocacy teaches that each tactic was designed to drive the point of competition away from substitution and into a branded-product, marketing-driven marketplace. While the initial campaign asserted that biosimilars and interchangeable biologics were impossible, and then evolved into arguments regarding mandating guidance and the need

Analytical Data As Foundation


- **Understand the molecule and function**
 - Identify critical quality attributes and clinically active components
 - Have support for assessment and approach
- **Before** proceeding with animal and clinical studies, generate **sufficient** analytical (structural and functional) data to:
 - Characterize reference product variability and product quality characteristics
 - Characterize proposed biosimilar product quality characteristics
 - Identify and evaluate impact of differences
 - Don't ignore or sweep under the carpet
 - Must be **highly similar** and no clinically meaningful differences



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The Question(s) Should Drive The Study Design

- Don't think in “Phased Development” terms (Phase 1, 2, and 3 studies)
- When considering designing a study, **evaluate and understand the question** you are trying to answer
 - What is the residual uncertainty?
 - What analytical differences have been observed and how best to evaluate the potential impact?
 - What will the data tell you? Will it answer the question?
- Provide a **sound rationale** for methods, assays, design, analyses, etc.
 - **Understand** the tools, including any limitations



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for originator data from large safety and efficacy trials, we believe that the opponents have always understood that innovation was possible. Their major goal, however, was to engage with physicians, patients and the political and regulatory communities to raise “concerns” that would facilitate the creation of a legal and regulatory scheme that favored marketed products and prevented or made difficult generic-like substitution.²⁰ In our 2008 comments to the FTC following the November 21, 2008 Roundtable, we made the comment that the law should not be used to put a limit on innovation,²¹ and we believe that a fair examination of the history and the on-going opposition tactics makes plain that they are just another example from this playbook.

2. State substitution restriction proposals are designed to interfere or prevent investment in the innovation needed to make the interchangeable biologic part of the biosimilar pathway a success.

When the previous efforts failed to (A) keep the interchangeability provisions out of the BPCIA and (B) cause the FDA to implement regulatory policy that would have stifled the opportunity to develop and launch interchangeable biologics, anti-substitution advocacy shifted to the States. We believe that opponents are now focused on substitution restrictions because substitution enables sales without the need for marketing and maximizes the affordability of a medicine after exclusive rights expire. The BPCIA authorized the FDA to make determinations of interchangeability for precisely this purpose. The law expressly provides that a physician is not needed to intervene in a dispensing decision, and contemplates that there may be no need to market a product. In fact, it is likely that any marketing claims that assert there are any meaningful differences or advantages in a brand product versus an interchangeable biologic products would be unlawful promotion of a false superiority claim that is not in any approved FDA labelling. Similarly, a claim by a biosimilar manufacturer that its clinical data somehow

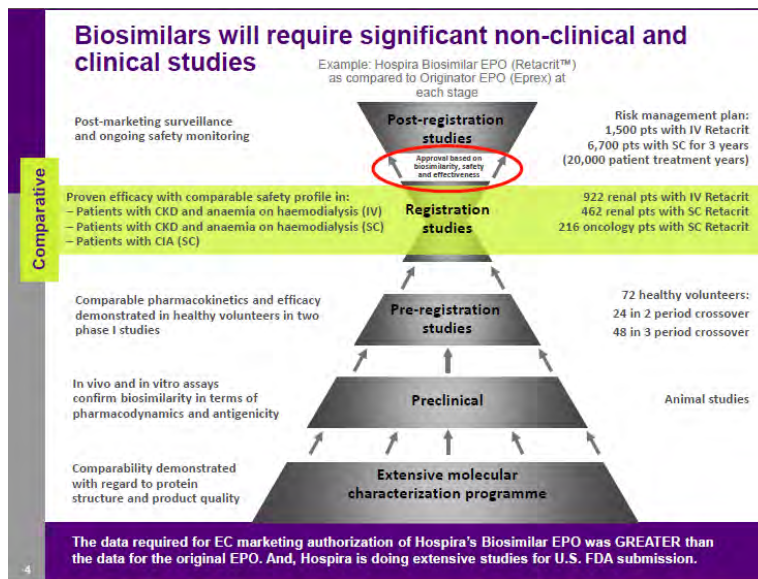
²⁰ In Europe, the EMA regulatory staff have authored articles recently for the purpose of responding to brand industry claims that biosimilars were different and that the differences raised concerns. These articles made the point that the differences between the approved biosimilars in Europe were no different from the brand than the brand was to itself from lot to lot. Martina Weise, Marie-Christine Bielsky, Karen De Smet, Falk Ehmann, Niklas Ekman, Gopalan Narayanan, Hans-Karl Heiml, Esa Heinonen, Kowid Ho, Robin Thorpe, Camille Vleminckx, Meenu Wadhwa, Christian K Schneider, (members of the Biosimilars Working Party of the European Medicines Agency), Biosimilars – Why Terminology Matters, 29 Nature Biotech 690 (August 2011); Christian K Schneider, Camille Vleminckx, Iordanis Gravanis, Falk Ehmann, Jean-Hugues Trouvin, Martina Weise & Steffen Thirstrup, Setting the stage for biosimilar monoclonal antibodies, 30 Nature Biotech 1179 (December 2012).

²¹ Comments of Momenta Pharmaceuticals, Emerging Health Care and and Competition and Consumer Issues; FTC Project No. P083901 (December 22, 2008).

made its biosimilar product safer or better would violate the same promotion prohibitions.²² But this is precisely the effect of state substitution restrictions. It prompts physician intervention, and puts the state in the position of “counter-detailing” to physicians that differences exist between an interchangeable biologic and the reference product. It would most likely make it necessary to engage in marketing to sell interchangeable products, and may even cause companies to conduct additional or larger clinical trials to address these “fears” and “concerns” when the FDA has concluded the product is interchangeable and additional clinical trials are not necessary.

Thus, restrictions on substitution are designed to force interchangeable biologic companies to market their products to physicians, when the express purpose of the law was to approve the product for substitution at the pharmacy without the need for intervention of a physician. No one is debating that a prior authorization would interfere with pharmacy substitution and would require physician intervention. Yet, discriminatory record keeping, notice and other requirements, would similarly interfere with substitution by putting dispensing barriers in place that would cause a pharmacist not to substitute without prior authorization. Krystalyn Weaver, Pharm.D., made this point crystal clear when, in response to a question about the effect of 10-day post-notification “compromise,” she stated that post-notification (even 10-day post notification) would be no different in effect than pre-substitution notification of the physician. She confirmed that a 10-day post-dispensing notification *would cause a pharmacist to seek pre-substitution authorization* and the reason was clear and demonstrable: Biologics are

²² At the same time, some companies may choose to use clinical data to explain why residual uncertainty associated with structural differences does not create any meaningful clinical differences. For example, extensive clinical data may be required to demonstrate biosimilarity where significant uncertainty about structural differences. Hospira provided an example of this approach in its presentation at the Workshop:



If, however, the clinical data were used to claim that another biosimilar or interchangeable product did not have a degree of structural difference necessitating such trials, and was somehow suspect for not having extensive clinical data, when in fact the reason targeted clinical data for the second product is due to a lower level of residual uncertainty, then we believe such claims would also be a violative promotional marketing claim.

extraordinarily expensive²³ and are not returnable. As a result, a pharmacist would not take the risk of the financial exposure for dispensing an interchangeable biologic without obtaining pre-authorization.

In addition to the notification requirements in these bills, the proposed language pertaining to “interoperable medical records” appears to be carefully chosen to further disrupt the opportunity for substitution at the pharmacy. The Washington State bill S-3095, for example, contained language requiring that:

...the pharmacist or the pharmacist’s designee shall ... (a) Record the name and manufacturer of the product dispensed in an interoperable health records system shared with the prescribing practitioner, to the extent such as system is available; or in the case that an interoperable health records system is unavailable; (b) [provide special notice to the prescriber].

On its face it sounds simple and the language has been “marketed” to legislators by suggesting that notices will be rare because interoperable medical records are widely available. In fact, interoperable medical records are not well-defined and generally refer to a patient’s complete medical record as opposed to a record of dispensed medicines. As noted by pharmacy representatives at the Workshop, it will not be clear to a pharmacist (and may not be possible for a pharmacist to know) if an interoperable medical record system is available to a physician, and may not be in place at many pharmacies. What is in place and available nationwide for free to physicians today, are interoperable ePrescribing systems which contain prescription dispensing records (not complete health records), which is the precise information needed to conduct effective pharmacovigilance. This is a far more innovative and reliable method for informing physicians than “communication by any means” to the physician.

²³ AARP, among others, testified at the Workshop regarding the increasing proportion of medicines that are biologics and in particular the high product costs:

Treatment costs are extraordinarily high

- On average, biologic drugs are 22 times more expensive than traditional drugs⁴
- The average annual cost of a branded biologic is estimated to be \$34,550⁵
- Annual costs can range from \$25,000 to \$200,000 or more⁶



AARP | 5

The burdensome effect of these provisions would likely force an interchangeable biologics manufacturer to engage in otherwise unnecessary marketing and sales activity to overcome the barrier and allow for the substitution. It would in effect reverse the competitive advantage of an interchangeable designation. It would re-elevate physician intervention in direct conflict with the BPCIA interchangeability standard and achieve the opposition's goal of rendering the interchangeability designation non-competitive.

As noted at the Workshop, the advocacy of the so-called "compromise" position by several biosimilar companies is best explained by these effects on competition. The biosimilar companies that are advocating the so-called compromise, are generally companies that have developed products first in Europe, where interchangeability is not an approval standard, and which does not authorize pharmacy substitution. They are likely seeking to introduce those products in the United States as well – a pro-competitive activity – and have limited incentive to restart development to meet an interchangeability standard. What is anti-competitive, however, is the effort to impose a sales and marketing based barrier to entry of interchangeable biologic competition. While non-interchangeable biosimilar products, which are considered "new active ingredients," will have to be marketed because they are not substitutable, as is the case in Europe, there is the possibility for cost savings and a greater level of competition in the United States due to the availability of the interchangeable biologic designation. We believe that a careful examination of the facts and circumstances will show that many of the biosimilar companies that have aligned with the reference brand manufacturers to support substitution restrictions have likely done so because they intend to sell and market branded products --- even if interchangeable --- and also see a competitive advantage in preventing substitutable interchangeable biologic competition or deterring such competition by forcing interchangeable biologics firms seeking to rely on substitution to market their products too.

We also believe that the restrictions on interchangeable biologics, and the attempt to enact discriminatory provisions into state law, are part of the historic disinformation campaign to disparage interchangeable biologic competition generally. Notice provisions deliver a message that interchangeable biologics really are not substitutable like generics; that they are somehow different and risky. This is a message that as noted earlier would be an unlawful comparative claim in the marketing setting, but when adopted as a restrictive state substitution law would enlist the State in this anti-substitution marketing campaign. It also provides a forum for publicizing a

Legislation Against Biosimilars: Brand Company-supported Bills Were Appropriately Questioned

The New York Times
Tuesday, January 29, 2013 1:07 PM EST 5:44 AM ET
Billions at Risk, Firms Lobby States to Limit Generics
By ANDREW POLLACK
The biotechnology industry's lobbying effort could blunt new competition to its products and reduce the savings anticipated in the federal health care overhaul.

Los Angeles Times OPINION
Battle over 'biosimilars'
States shouldn't stand in the way of cheaper versions of biologic drugs the FDA deems safe.

The New York Times
Editorial: Improper Efforts to Limit Competitive Drugs
February 9, 2013

Drug Industry Daily
Feb. 25, 2013 | Vol. 12 No. 39

Hamburg Defends Biosimilar Substitution, Says Efforts to Undermine Trust Are 'Worrisome'
ORLANDO — FDA Commissioner Margaret Hamburg defended the substitutability of interchangeable biosimilars, saying that attempts to undermine trust in the products are "worrisome and represent a disservice to patients who could benefit from these lower-cost treatments."

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message to physicians that cannot be made in the sales and marketing context. As noted at the Workshop, the FDA and the press have recognized the troublesome nature of the campaign to undermine trust in FDA approvals and assert that interchangeable biologics are not really substitutable but are just “biosimilars” and are “different”. This writes the “not a new active ingredient” distinction in Section 351(n) out of the BPCIA.²⁴

Finally, the advocates of special notice provisions respond by asserting that it is a bona fide effort to ensure there is “transparency” regarding pharmacy dispensing, and that physicians have a right to know and want to know what is dispensed to ensure that adverse events are properly attributable to the right manufacturer. This argument fails in multiple respects.

First and foremost, all companies support transparency of, and access by physicians to, pharmacist dispensing records. The pharmacist community has established and has in place nationwide recordkeeping of dispensed medications, and includes this information in nationwide ePrescribing systems. These systems offer physicians real time access to patient dispensing records, without charge, and provide a complete picture of the prescription record including the



NDC number that specifies manufacturer, lot as well as product information. This makes it possible to determine which lot of any product was dispensed so that adverse events related to a manufacturing change of any manufacturer can be investigated. Special notice and different names for biosimilars do not achieve this objective. ePrescribing systems also provide a physician (should it be desired) information on all other products dispensed

previously to a patient so that medication conflicts and errors and can be avoided and identified. Importantly, a physician can access the data at no cost through the National ePrescribing Patient Safety Initiative. Thus, all a special notice or different name would do is confuse physicians when it is already possible for a doctor to know what was dispensed on a real time basis. Moreover, the special notice provisions do not provide information on manufacturer lot number for a brand product or for a biosimilar, nor for the interchangeable biologic. If the real objective of these proposals was to make pharmacovigilance more effective, then the special notice does little to achieve that end. Instead, it allows the advocates of state law restrictions *to speak about safety and raise “concerns,”* and to do so in the context of biosimilars and interchangeable biologic substitution. Transparency is not a valid argument for these restrictions.

²⁴ See note 2, above.

Similarly, safety is not a valid basis for these special notice or other restrictions. First, the better means for tracking and investigating all products would be through the use of the NDC number which identifies the manufacturing lot for every product and, when coupled with manufacturer name, provides proper identification. The EPREX investigation referred to by Amgen at the Workshop is an excellent example. Had the company contacted the physician and the physician been able to look at an ePrescribing system (which was not in place in Europe), it would have known it was another manufacturer's product that caused the adverse event, and, more importantly, would have known the lot number. The lot number could then have been immediately associated with a manufacturing change and the cause more easily identified as a stopper change. What is ironic is that companies developing biosimilars, and even more so interchangeable biologics, have an incentive to thoroughly characterize their products to assure quality through state of the art technology, and do not rely to the same extent on the product is the process. The more one knows what is in the vial, the more likely one is able to prevent the adverse event from occurring in the first place. By enacting state substitution law restrictions, the incentive to develop the safety enhancing technology is diminished as the benefit from doing so, interchangeability, is diminished.

Finally, advocacy based on a need for "transparency" can be easily misused in the legislative context through leading questions. If a physician is asked, do you want to know what your patient was dispensed, it is no surprise that the physician responds yes. Human nature encourages us to respond that we want to be informed, when asked. What was telling, however, is the real world experience of Express Scripts cited at the Workshop. As noted by Dr. Miller in his presentation, when the dispensing information was offered to physicians from Surescripts automatically (like a special notice), it was rejected as undesirable or unnecessary information.²⁵ This suggests that the special notice provisions will have multiple negative commercial effects on competition from interchangeable biologics. First, if the notice is not received on request at the time of dispensing, it will be viewed as an annoyance and waste of office staff time. Second, it will deliver a message of caution and concern because they do not arrive when biosimilars or brands are prescribed or undergo manufacturing changes. Finally, the so-called compromise form of special notice permits any form of communication (phone call, email, voicemail, text, etc.), so it is not clear that one could know whether the message is even received, or if received, stored in a record that would be accessible should there be a need to use the information. Why? The proponents of special notice have a different objective: to erect barriers to interchangeable biologic competition.

We believe the evidence is clear. Federal policy should opposing anti-competitive state substitution laws that violate the BPCIA. State substitution laws conflict with the BPCIA when they require:

- Prior authorization or intervention by a physician for substitution of interchangeable biologics at the pharmacy; or
- Notice to a physician of substitution (pre- or post –dispensing) because in practice it will cause a pharmacist to seek prior authorization to avoid the risk of financial loss on dispensed interchangeable biologics.

²⁵ Testimony of Steve Miller, M.D. at Workshop.

The unmistakable effect of these restrictions will be to erect barriers to competition from substitution and require marketing and sales to promote interchangeable biologics based on clinical data. The investment in interchangeability innovation will not be warranted if the competitive advantage of avoiding sales, marketing and clinical costs is lost or significantly diminished. Congress intended to spur innovation in this area by enacting an interchangeable designation, not deter it.

The need for transparency and for pharmacovigilance is best assured by addressing all medicines not spotlighting the concern and applying it to single category of products. By using existing innovation in ePrescribing systems that record more comprehensive information than a “communication” that could be misplaced or not recorded, it avoids the anti-competitive impact and addresses the problem more appropriately.

In short, we asked the FTC at the Workshop to find, and ask that this Committee:

- Find that state substitution restrictions are anti-competitive and are not the least restrictive alternative for ensuring transparency and promoting innovation; and
 - Encourage the FDA or HHS to issue guidance that state substitution restrictions violate the express provisions of the BPCIA because they would cause, without demonstrable benefit, the intervention of a health care provider in an approved pharmacy substitution decision in conflict with Section 351(i).
3. The campaign to assign different non-proprietary names to biosimilars and interchangeable biologics is also part of a commercial campaign to claim biosimilars are different.

No one disputes that under Section 351(k), a biosimilar will receive rigorous FDA review

and must be shown to be highly similar to the reference product and not to have any clinically meaningful differences. This means that a non-interchangeable biosimilar is safe and effective for use in its approved indications. As with generic drugs in the early years following Hatch-Waxman, there is an effort to assert that we need to be “careful,” that we should have “concerns about patient safety,” and that biosimilars are not really “biosimilar” but are

different. Websites of the proponents of differential naming are replete with this type of messaging.

Similar anti-biosimilar campaigns have been employed in Europe and, as reported by Hospira and Sandoz at the Workshop, the EMEA has rejected requests for differential naming for biosimilar products.

EMA Initiated Education to Address Unfounded Concerns about Biosimilars

Biosimilars in rheumatology: the wind of change

Christian K Schneider

Correspondence to Dr C K Schneider, Danish Health and Medicines Authority, Medicines Assessment and Clinical Trials, Copenhagen 2300, Denmark, and Twincote Centre for Experimental and Clinical Infection Research, Hanover, Germany; cks@dkmadk

...no batch of any reference product is 'identical' to the previous one—'non-identity' is a normal feature of biotechnology that has to be controlled by tight specifications of critical product attributes, within current technical and scientific limitations (inherent variability). The 'art' for a biosimilar is to demonstrate that the biosimilar is as close as possible to its reference product in all relevant functional and structural aspects.

...What is often not mentioned is that originator mAbs/cepts have undergone changes after their approval—this is what regulators call the 'life cycle' of a medicine.

Ann Rheum Dis March 2013 Vol 72 No 3



Christian Schneider, the head of the Biosimilar Working Party Group at the EMEA, published an article last year clearly stating that the differences cited in biosimilars is inherent in all biologics and should not be a basis for asserting a reference product versus biosimilar distinction.²⁶

Pharmacovigilance is also raised as a "concern" – i.e., that somehow pharmacovigilance is impaired by having a shared non-

proprietary name. This argument fails for all of the reasons cited in section 2 with regard to state substitution restrictions²⁷ and for additional reasons as well.

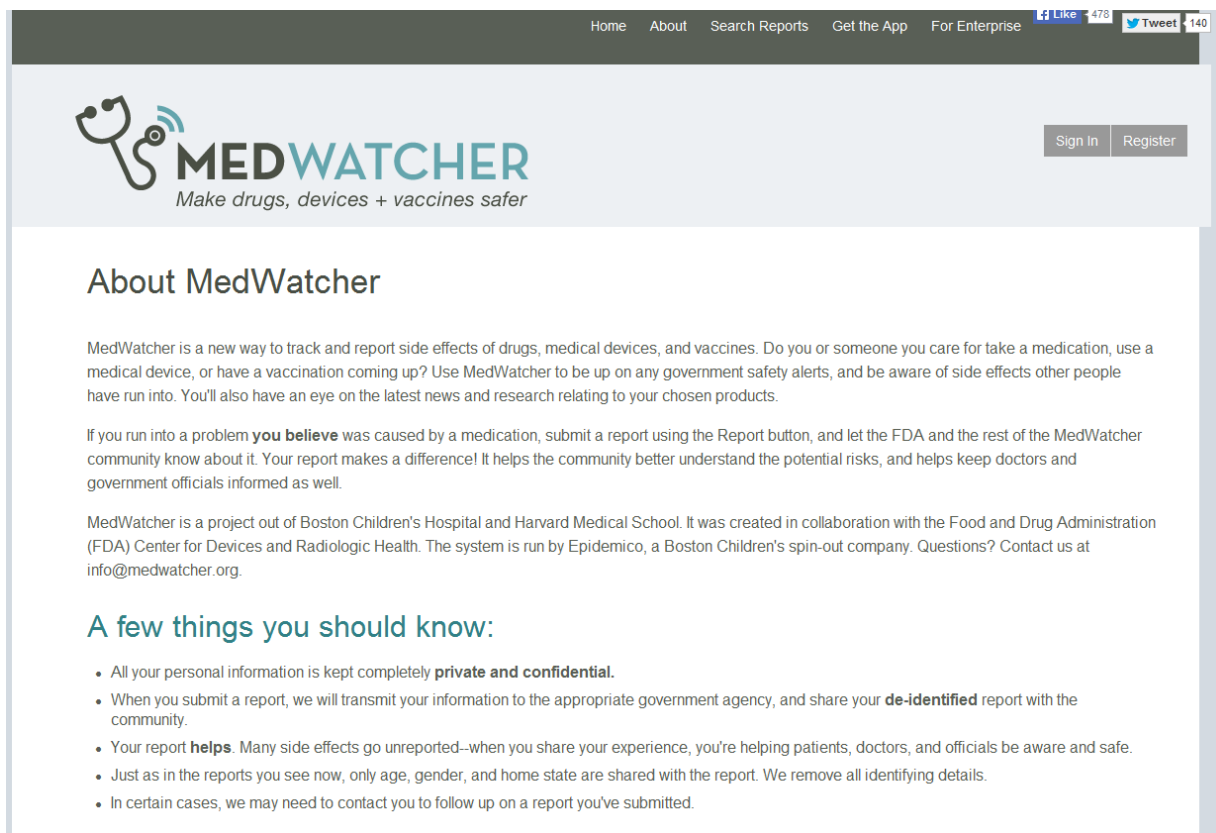
The data relied on by Emily Alexander at the Workshop to support differential naming cites the use of brand names by physicians reporting adverse events associated with a generic drug. As discussed at the Workshop, doctors frequently prescribe drugs by the brand name (knowing substitution will occur). Thus, when they report an adverse event associated with a patient, it should not be surprising that the adverse event is reported as a brand product adverse event. The fact that this occurs is well-known and from signal detection purposes is good because the reference brand product company holds the most comprehensive safety database having conducted the original clinical trials, and is in the best position to investigate trends or rare events across all substitutable drugs. The brand company also has primary labelling responsibility. As part of the investigation, the reporting company would report this to the FDA, which maintains a central database, and would/should call the physician (who can call the pharmacist or look in an ePrescribing database like Surescripts) to see what was dispensed to determine if substitution occurred and which product was dispensed to rule out or identify a product quality as opposed to a mechanism of action defect. It is misleading to cite this phenomena as a basis for requiring different names.

By having different non-proprietary names, physicians wrongly assume that related mechanism of action adverse events across multiple biosimilar or interchangeable biologic products are not related, making it more difficult to catch rare but important safety signals.

²⁶ See note 15, above.

²⁷ See pages 16-17, above.

Perhaps more importantly, for biologics (each of which is inherently variable), it ignores the most relevant challenge (i.e., that biologics are variable and undergo manufacturing changes). It would provide a false sense of assurance to rely on non-proprietary name rather than properly investigate and identify with the pharmacist a biologic's lot number to see if it was a manufacturing change that triggered the adverse event. By assigning different names, a lack of efficacy in a patient that is continuously on the same product might be ignored and assumed to be a normal progression of the disease, and a signal missed, but if the name was different and the lot number not checked, it might be presumed, incorrectly, that a change to a biosimilar or interchangeable biologic was the assignable case, again causing a signal to be missed. By using the NDC number in all cases, the investigation would identify the relevant information to best assure patient safety and that is what is stored nationwide in pharmacy systems and is now available without charge to physicians.



The screenshot shows the MedWatcher website. At the top, there is a navigation bar with links for Home, About, Search Reports, Get the App, and For Enterprise. On the right side of the navigation bar, there are social media icons for Facebook (478 likes) and Twitter (140 tweets). Below the navigation bar is the MedWatcher logo, which features a stylized stethoscope and the text "MEDWATCHER" in a bold, sans-serif font. Underneath the logo is the tagline "Make drugs, devices + vaccines safer". To the right of the logo, there are two buttons: "Sign In" and "Register".

About MedWatcher

MedWatcher is a new way to track and report side effects of drugs, medical devices, and vaccines. Do you or someone you care for take a medication, use a medical device, or have a vaccination coming up? Use MedWatcher to be up on any government safety alerts, and be aware of side effects other people have run into. You'll also have an eye on the latest news and research relating to your chosen products.

If you run into a problem **you believe** was caused by a medication, submit a report using the Report button, and let the FDA and the rest of the MedWatcher community know about it. Your report makes a difference! It helps the community better understand the potential risks, and helps keep doctors and government officials informed as well.

MedWatcher is a project out of Boston Children's Hospital and Harvard Medical School. It was created in collaboration with the Food and Drug Administration (FDA) Center for Devices and Radiologic Health. The system is run by Epidemico, a Boston Children's spin-out company. Questions? Contact us at info@medwatcher.org.


A few things you should know:


- All your personal information is kept completely **private and confidential**.
- When you submit a report, we will transmit your information to the appropriate government agency, and share your **de-identified** report with the community.
- Your report **helps**. Many side effects go unreported—when you share your experience, you're helping patients, doctors, and officials be aware and safe.
- Just as in the reports you see now, only age, gender, and home state are shared with the report. We remove all identifying details.
- In certain cases, we may need to contact you to follow up on a report you've submitted.

There are also important data capture innovations underway that are increasingly available to physicians such as a Medwatcher smartphone APP. The Medwatch APP allows for a physician to use a mobile phone to take a picture and report adverse event information in realtime, facilitating identification of the product, the manufacturer, the NDC number and other critical information. We believe innovation is a far better means to address the concerns being raised that are in our view designed to negatively impact biosimilar and interchangeable biologic competition.

Lastly, the proponents of different names have failed to mention what may prove to be the most useful innovation for addressing pharmacovigilance: the FDA Sentinel Initiative. While ad hoc post-marketing information is vital to patient safety, and will continue to play an

FDA's Sentinel Initiative





Transforming how we monitor the safety of FDA-regulated products

A national electronic system that will transform FDA's ability to track the safety of drugs, biologics, and medical devices once they reach the market is now on the horizon. Launched in May 2008 by FDA, the Sentinel Initiative aims to develop and implement a proactive system that will complement existing systems that the Agency has in place to track reports of adverse events linked to the use of its regulated products.

Monitoring the safety of its regulated products is a major part of FDA's mission to protect public health. The Sentinel System enables FDA to actively query diverse automated healthcare data holders—like electronic health record systems, administrative and insurance claims databases, and registries—to evaluate possible medical product safety issues quickly and securely.

Sentinel will be developed and implemented in stages. As the system is being developed, data will continue to be managed by its owners and questions would be sent to the participating data holders. Within pre-established privacy and security safeguards, these data holders would evaluate their information and send summary results to FDA.

important role in patient safety, the Sentinel Initiative is aggregating comparative, controlled data on products from patient claims and outcome data from the nation's major hospitals, health care plans, insurance companies and PBMs. It enables rigorous review of the data and a proactive system for signal detection.²⁸ The Academy of Managed Care Pharmacies is also conducting a similar effort in collaboration with the Sentinel Initiative. According to the AMCP, the system

now captures data from approximately 75% of the patients in the United States and should provide the most reliable kind of information for safety signal detection through this innovative approach and could render the differential naming proponent's pharmacovigilance arguments moot.²⁹ For this reason, AMCP policy on biosimilar naming provides:

²⁸ From the FDA Sentinel Program Home Page <http://www.fda.gov/safety/fdassentinelinitiative/default.htm>

²⁹ Statement of Bernadette Eichelberger, PharmD. On February 18, 2014 at the Biosimilars Committee Meeting, Annual Meeting of GPhA. The Academy of Managed Care Pharmacy (AMCP) is a national professional association of pharmacists, health care practitioners and others who develop and provide clinical, educational and business management services on behalf of more than 200 million Americans covered by a managed pharmacy benefit. AMCP members are committed to a simple goal: *providing the best available pharmaceutical care for all patients*. Some of the tasks AMCP's more than 6,000 members perform include:

- Monitoring the safety and clinical effectiveness of new medications on the market;
- Alerting patients to potentially dangerous drug interactions when a patient is taking two or more medications prescribed by different providers;
- Designing and carrying out medication therapy management programs to ensure patients are taking medications that give them the best benefit to keep them healthy; and
- Creating incentives to control patients' out-of-pocket costs, including through lower copayments on generic drugs and certain preferred brands.

These practices, and more, aim to ensure that *all* patients can receive the medications they need to improve their health while at the same time keeping health care costs under control.

Manufacturers of approved biosimilars should be allowed to use the same government-approved name/international nonproprietary name as the reference product (e.g. epoetin alpha for Procrit®). This will hopefully ease confusion among prescribers and patients and help to encourage substitution of biosimilar products in appropriate instances. However, it is also important to continue to use current mechanisms such as manufacturer name, national drug code (NDC) numbers and lot numbers to effectively differentiate batches for safety monitoring purposes.³⁰

What is particularly troubling about the differential naming proposal is the confusion it would cause for interchangeable biologics, biosimilars that are determined by the FDA to be safe to substitute and switch. If a biologic is demonstrated to be substitutable, how could it not have the same name? Reference products undergo manufacturing changes and do not have to demonstrate interchangeability. If a different name is used, it will suggest that an interchangeable biologic is not substitutable. Similarly, there will be confusion when a physician writes a prescription with the non-proprietary name. Will it mean that a product must be “dispensed as written”?

It is also worth noting that many reference brand biologics today are approved under separate BLAs, are known and expected to be different, and share the same non-proprietary name. Examples include Kogenate (antihemophilic factor (recombinant) and Recombinate (antihemophilic factor (recombinant)). No one is asserting a safety concern as a result and we believe the opposite is the case because it has facilitated the capture of important product class safety information.

When the evidence is reviewed, and the arguments parsed, we believe it becomes clear that the primary rationale that motivates differential naming is to erect barriers to biosimilar and interchangeable biologic use. Sales representatives will then promote use of the unique name with brand names to reduce substitution. Pharmacy systems would have to be reprogrammed to accommodate different names. Marketing would be elevated in importance to capture prescription volume. At each step in the reimbursement and distribution and/or sales process, attention would have to be devoted to explaining why the name was different and why biosimilar or interchangeable was an acceptable alternative. Having this hurdle at the time the pathway is implemented is not pro-competitive.

We ask the Committee to review the data and appropriately report that differential naming proposals are anti-competitive and not in the interest of America’s health care consumers.

³⁰ Where We Stand on Biosimilar Drug Therapies, Academy of Managed Care Pharmacies, <http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=16640> .

Summary and Conclusion

We appreciate the opportunity to provide written comments to the Committee regarding the 21st Century Cures initiative. We anticipate that many will comment more narrowly on the need for new cures. All of us support innovation. History teaches that one of the best means available to Congress to spur innovation is to create competition to non-innovative research and development and steer investment to invention of new cures. Hatch-Waxman did this for drugs and was a major initiator of the biotechnology revolution. The United States became the world leader in biotech as a result. The BPCIA should do the same by facilitating innovative development and commercialization of biosimilars and interchangeable biologics. Our global leadership is at stake. And more importantly, innovation will lead to safer biologics, enhanced quality, and investment in new cures while making medicine more accessible and affordable.

To do this, we believe that:

- Biosimilar and interchangeable biologic policy should be driven and measured by how it:
 - Promotes innovation and attracts investment in delivering safe, effective and affordable biologics
 - Addresses patient needs (including access) and patient safety
 - Avoids using the least innovative and most anti-competitive solutions to achieve these important objectives.
- The opposition to biosimilar and interchangeable biologic competition have much to lose financially when patents and exclusivity expire for a brand product
 - Financial loss and risk is what really motivates the proposals for state substitution restrictions and naming barriers to biosimilar and interchangeable biologic competition
 - State substitution restrictions and differential naming will create barriers to investment in the innovation necessary to provide access to safe, effective and affordable biologics
 - The loss of competition will decrease the incentive for brand companies to innovate the next generation of new cures if patent or exclusivity profits continue after expiration or loss of exclusivity
- Federal policy should therefore encourage the FDA or HHS to adopt a policy stating that:
 - State substitution restrictions are an unlawful conflict with Section 351(i) of the BPCIA; and
 - The benefits of innovation already underway from ePrescribing, the Sentinel Initiative and other programs, and the confusion that naming differences would cause, mean that biosimilar and interchangeable biologics should share the same non-proprietary name

21st Century Cures
House Energy and Commerce Committee
June 3, 2014
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Thank you for your consideration of our views.

Sincerely,



Bruce A. Leicher
Senior Vice President and General Counsel

MOMENTA



Anti-Competitive Deterrents to Investment and Innovation in Biosimilars and Interchangeable Biologics

*Follow-On Biologics Workshop
Bruce A. Leicher, Sr. Vice President and General Counsel, Momenta Pharmaceuticals Inc.
Federal Trade Commission February 4, 2014*



Corporate Overview

- Biotech company founded 2001 based on technology developed at the MIT for the precise understanding of complex mixture medicines
- 250+ employees located in Cambridge, MA
 - Substantial Growth (100+) in Employment due to new Biosimilar Pathway
- Expertise in high-resolution analytics, biological characterization, and process engineering



Introduction

- Biosimilar and Interchangeable Biologics policy should be driven and measured by how it:
 - Promotes Innovation and Attracts Investment
 - Addresses Patient Needs and Patient Safety
 - Avoids using the least innovative and most anti-competitive solutions to achieve these objectives
- The opposition to Biosimilar and Interchangeable Biologic Competition:
 - Is the central factor that motivates restrictions on substitution of Interchangeable Biologics
 - Undermines the attractiveness of investment in, and access to, safer, more affordable biologics
- The related commercial campaigns to require different non-proprietary names, and to restrict access to brand product for FDA-regulated biosimilarity and interchangeability testing are designed to impede investment in, development of, and competition by, safe and affordable Biosimilars and Interchangeable Biologics.

3

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A Long Established Campaign Against Biosimilar Innovation and Competition

Tactic	Message	Barriers to Competition
BIO CP - 2003	<ul style="list-style-type: none"> • Generic Biologics are Impossible 	<ul style="list-style-type: none"> • Prevent Regulatory Approval • Prevent/Deter Legislative pathway
Oppose Biosimilar Pathway - 2	<ul style="list-style-type: none"> • Biosimilars are unsafe even if possible • Interchangeable biologics are impossible/different 	<ul style="list-style-type: none"> • Prevent/Deter pathway • Incorporate legislative features that prevent/deter use of the pathway <ul style="list-style-type: none"> • Mandatory Clinical Trials • Complex IP exchange
Influence FDA Guidance - 2011	<ul style="list-style-type: none"> • Same messages 	<ul style="list-style-type: none"> • Emphasize differences (Eg. Naming) • Mandate Unnecessary Clinical trials • Freeze scientific standards for similarity and interchangeability
Abbvie CP	<ul style="list-style-type: none"> • Same messages 	<ul style="list-style-type: none"> • Delay Biosimilars for 10 years
Naming Campaign JnJ Citizen Petition	<ul style="list-style-type: none"> • Biosimilars are different and raise safety concerns 	<ul style="list-style-type: none"> • Amplifies anti-biosimilar commercial campaign with providers, payors, patients and regulators
Restricted Access to Reference Products	<ul style="list-style-type: none"> • Biosimilar companies are irresponsible 	<ul style="list-style-type: none"> • Prevents/Delays initiation of development

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The State Substitution Campaign is the Next Tactic to Prevent and Restrict Competition from Interchangeable Biologics

- Interchangeable Biologics were adopted and embraced in the BPCIA
- The opposition failed at the Federal Level and now seeks to use the same anti-competitive messages to enact laws that will deter or prevent investment in Interchangeable Biologics
- The BPCIA is clear, and is even clearer than Hatch-Waxman, in that it expressly provides:

“the [interchangeable] biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product” (emphasis added).

- Yet, the States are being asked, in effect, to join in a commercial marketing campaign to
 - Disparage Interchangeable Biologics
 - Restrict substitution; and
 - Provide notice to doctors to intervene and be concerned about FDA approved biologics

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Why is Substitution so Important?

- Substitution eliminates the need for sales and marketing to physicians and payors
 - Note that some biosimilar companies now support a so-called “compromise”
 - Note also that each of these biosimilar companies
 - May not be seeking to develop interchangeable biologics, and/or
 - May plan to market their biosimilars and interchangeable biologics with a sales force, and
 - Thus benefits from preventing substitution to protect pricing and profits in their branded and “marketed” biosimilar business
- Substitution provides for the highest level of access and affordability to medicines after patents and exclusivity expire
- Substitution enables a return on investment for the substantial innovation needed to develop Interchangeable Biologics that match the reference product

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Anti-Biosimilar déjà vu: State Substitution Restrictions are Designed to Restrict Competition, Not Improve Safety or Knowledge

- Notice Provisions are designed to deliver a message that Interchangeable Biologics are “different” or “suspect” and give marketed products a competitive advantage
 - E.g., BIO appropriately opposes GMO labelling for just this reason
- Special notice and recordkeeping burden pharmacists to deter substitution and promote branded biologics and branded biosimilars
- This matters
 - To patients, who cannot access or afford life saving biologics
 - To physicians, who want transparent and reliable information from biologics manufacturers about all products
 - To payors, who cannot pay for biologics and other critical care
 - To novel developers, who rely on headroom in payor budgets from generics to pay for novel new medicines
 - To regulators, who want to promote quality by design innovation

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Legislation Against Biosimilars: Brand Company-supported Bills Were Appropriately Questioned

The New York Times

Tuesday, January 29, 2013 Last Update: 8:41 AM ET

Billions at Risk, Firms Lobby States to Limit Generics

By ANDREW POLLACK

The biotechnology industry's lobbying effort could blunt new competition to its products and reduce the savings anticipated in the federal health care overhaul.

Los Angeles Times | OPINION

Battle over 'biosimilars'

States shouldn't stand in the way of cheaper versions of biologic drugs the FDA deems safe.

The New York Times

Editorial: Improper Efforts to Limit Competitive Drugs
February 9, 2013

Drug Industry Daily

Feb. 25, 2013 | Vol. 12 No. 39

Hamburg Defends Biosimilar Substitution, Says Efforts to Undermine Trust Are 'Worrisome'

ORLANDO — FDA Commissioner Margaret Hamburg defended the substitutability of interchangeable biosimilars, saying that attempts to undermine trust in the products are “worrisome and represent a disservice to patients who could benefit from these lower-cost treatments.”

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Why Innovative Biosimilar and Interchangeable Biologics Matter For Patient Access

- **Brand Biologics are Expensive**
 - The average daily cost of a brand name biologic product is approximately 22 times greater than a traditional drug.
 - Biologics can cost as much as \$10,000 to several hundred thousand dollars per year.
- **Biologics are the Future of Medicine**
 - By 2016 it is predicted that eight of the top 10 products on the market will be biologics.
- **The Price of Brand Biologics Continues to Increase**
 - U.S. average annual spending growth from 2002 to 2007 was 16% for biologics, compared with 3.7% for drugs.



http://www.gphaonline.org/media/cms/General_Fact_Sheet_for_Biosimilars_FINAL.80913.pdf

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Anticipated Annual Changes in U.S. Spending on Traditional Drugs

Therapy Class	2013	2014	2015	3-Year Compounded Total
DIABETES	8.9%	6.8%	6.7%	24.1%
HIGH BLOOD CHOLESTEROL	-6.9%	-4.0%	-5.3%	-15.4%
HIGH BLOOD PRESSURE /HEART DISEASE	-7.2%	-5.9%	-6.0%	-17.9%
ASTHMA	-7.3%	0.8%	1.3%	-5.4%
ULCER DISEASE	-5.6%	-6.4%	-13.2%	-23.3%
DEPRESSION	-4.7%	-8.7%	-6.5%	-18.6%
ATTENTION DISORDERS	4.4%	10.0%	8.6%	24.8%
MENTAL/NEUROLOGICAL DISORDERS	-7.4%	-1.8%	-5.7%	-14.2%
PAIN	-3.3%	-4.5%	-4.2%	-11.6%
INFECTIONS	-6.9%	-6.8%	-6.0%	-18.4%
OVERALL TRADITIONAL	-1.0%	-1.7%	-1.4%	-4.1%

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Anticipated Annual Changes in U.S. Spending on Specialty Drugs (Many are Biologics)

Therapy Class	2013	2014	2015	3-Year Compounded Total
INFLAMMATORY CONDITIONS	25.1%	17.2%	17.4%	72.2%
MULTIPLE SCLEROSIS	19.8%	18.5%	16.8%	65.6%
CANCER	21.3%	20.9%	21.0%	77.4%
HIV	9.2%	9.6%	9.4%	30.9%
HEPATITIS C	33.0%	58.5%	168.4%	465.8%
GROWTH DEFICIENCY	6.2%	5.9%	6.5%	19.9%
ANTICOAGULANT	-0.3%	-0.2%	0.0%	-0.6%
PULMONARY HYPERTENSION	11.0%	11.1%	10.5%	-14.2%
RESPIRATORY CONDITIONS	24.8%	29.5%	27.9%	36.3%
TRANSPLANT	-2.2%	1.0%	-1.2%	-2.4%
OVERALL SPECIALTY	17.8%	19.6%	18.4%	66.8%

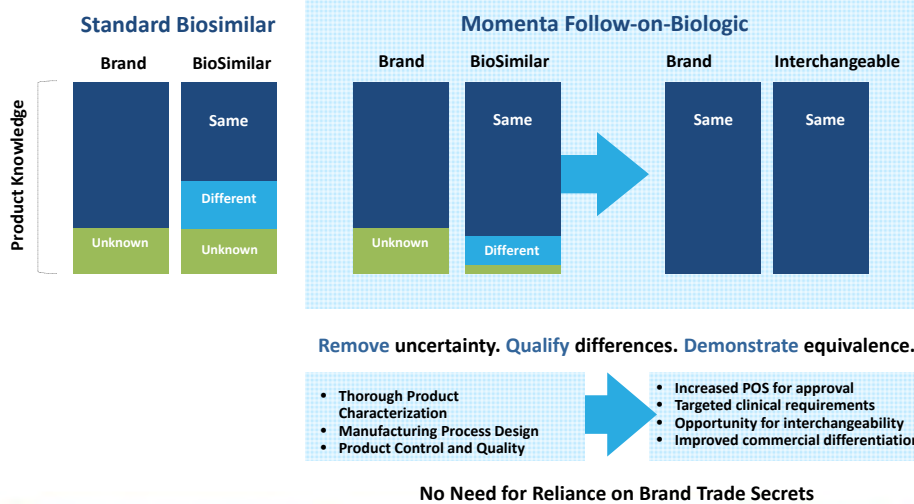
5.21.13 | Glen Stettin, MD
Specialty Drug Spending to Jump 67% by 2015

HEALTHCARE INSIGHTS
FROM THE EXPRESS SCRIPTS LAB

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Innovation is the Best way to Create Access to Safe, Affordable Interchangeable Biologics



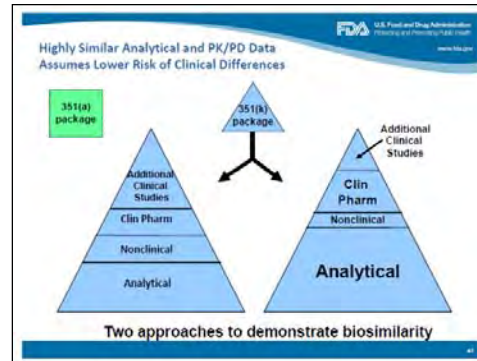
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The FDA Spurs Investment by Promoting Innovation

Approval Standards are Rigorous

- Biosimilars must:
 - Be Highly Similar to the Reference Product
 - Not have clinically meaningful differences
 - Interchangeable Biologics must also:
 - Be expected to perform the same in any given patient
 - Have the same risk associated with switching as the reference product
- And Most Importantly:
- Are By Statutory Definition, Substitutable at the Pharmacy without the Intervention of a Physician

Approach Drives Understanding of what Biologics Are: The Product is not Merely the Process



The Experience with Generic Lovenox is Relevant to the Development of Biosimilars



PERSPECTIVE

Scientific considerations in the review and approval of generic enoxaparin in the United States

Sau Lee¹, Andre Rava¹, Lawrence Yu¹, Robert Lionberger¹, Naiqi Ya¹, Daniela Verthelyi², Amy Rosenberg², Steve Kozlowski², Keith Webber² & Janet Woodcock²

VOLUME 31 NUMBER 3 MARCH 2013 NATURE BIOTECHNOLOGY

“Although it [Momenta’s generic Lovenox] is ... regulated under [the Food, Drug and Cosmetic Act], it was perhaps one of the most complex reviews imaginable, and it’s a superb example of how physiochemical studies could let us approve a generic drug,” Sherman maintained. “We still needed [non-clinical] immunogenicity studies, so we still needed some information, *but that’s about as complex probably as we expect that our average biosimilar application is going to be, and I think it’s a great illustration of the current state of the science and what we hope to be able to do with these applications.*”

– Rachel Sherman MD, Director of the Office of Medical Policy, CDER



Friday, February 10, 2012

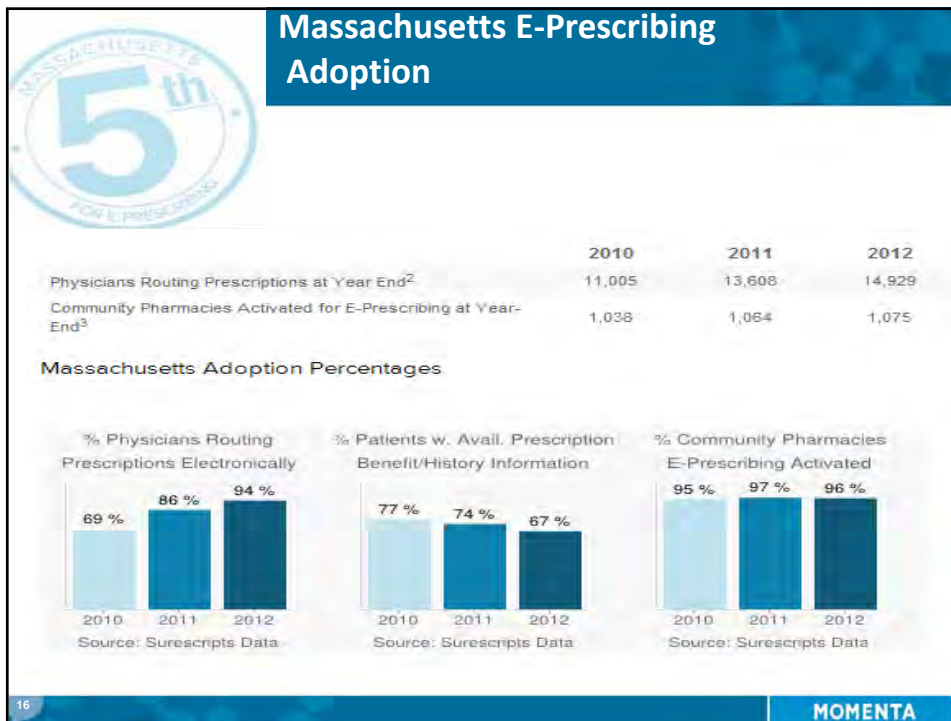
Biosimilars: Similarities to Enoxaparin and the Elephant in the Room

Innovation is the Pro-Competitive Way to Provide Substitution Transparency

- Special notification proponents argue for special notice under the guise of transparency - Why? Special Notice
 - Favors marketed brand and biosimilar products
 - Restricts and disparages substitutable Interchangeable Biologics
- Nationwide ePrescribing networks provide comprehensive transparency without restricting competition
 - Surescripts provides real time access to all dispensed medications and improves patient safety without discouraging substitution
 - Surescripts access is free to all physicians through the National ePrescribing Patient Safety Initiative
 - Any doctor can access and see what was dispensed
 - It reduces prescription conflicts and errors as well
 - ePrescribing is universally available and can be used even if a physician writes a prescription on paper

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National ePrescribing Patient Safety Initiative



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The National ePrescribing Patient Safety Initiative (NEPSI) is a joint project of dedicated organizations that each play a unique role in resolving the current crisis in preventable medication errors.

Electronic prescribing (ePrescribing) is a viable solution to counter shortcomings of the current paper-based prescribing processes that are in large part responsible for these errors. However, accessibility and cost barriers have slowed adoption of ePrescribing by providers.



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State Pharmacy Substitution Bill In Massachusetts

- Encourages Investment and Innovation in Safe and More Affordable Interchangeable Biologics:
 - Authorizes Pharmacist Substitution of Interchangeable Biologics
 - Relies on Electronic Medical Records to ensure Physicians aware of the biologic their patient receives
 - Avoids “disparagement” of biosimilars and interchangeable biologics
 - No physician intervention required
 - No prior notice required
 - No special record keeping is required
 - Substitution is handled in the same manner as generic substitution
 - Promotes Cost Effective Patient Access
 - Uses Innovation to develop Interchangeable Biologics and to Inform Physicians
 - Avoids Anti-Competitive practices
- Today’s science allows for demonstration that biologics are the “same”. (*Professor William S. Hancock, Barnett Institute of Chemical and Biological Analysis, Northeastern University, MassBio Policy Leadership Breakfast (January 23, 2013)*).

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CA Bill Vetoed



“Senate Bill (SB) 598 would affect two changes to our state’s pharmacy law. First, **it would allow interchangeable “biosimilar” drugs to be substituted for biologic drugs**, once these interchangeable drugs are approved by the FDA. **This is a policy I strongly support.**

....Second, it requires pharmacists to send notifications back to prescribers about which drug was dispensed.**to require physician notification at this point strikes me as premature.**

....I am returning SB 598 without my signature.”

—Edmund G. Brown Jr., Governor of California

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The FTC Should Adopt a Policy Opposing Anti-Competitive State Substitution Laws

- State Substitution Conflicts with the BPCIA and Restricts Competition when they require:
 - Prior intervention by physician for substitution
 - Prior notice to provoke intervention by physician before substitution
 - Subsequent notice to provoke intervention by physician and discourage substitution
 - Notice would be used by brand sales representatives to say Interchangeable products are different (code for an unproven safety risk)
 - Interchangeable Products would need sales and marketing support to compete (causing increased costs for consumers)
- Restrictions will deter critical investment required to Innovate and Develop Interchangeable Biologics
 - We should not pass laws that put a ceiling on innovation
- Special Notification is unnecessary and will discourage use of ePrescribing that appropriately ensures access to transparent dispensing information by physicians
- The FTC should encourage the FDA or HHS to Adopt a Preemption Policy to Preclude State Substitution Conflicts and Promote Consistency with the Definition of Interchangeability under the BPCIA

“[an interchangeable] biological product *may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product*” (emphasis added).

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Biosimilar and Interchangeable Biologic Non-Proprietary Naming

- Biosimilars are carefully reviewed and approved by the FDA
 - Biosimilars must be highly similar and have been shown not to have clinically meaningful differences
 - Interchangeable Biologics must also be demonstrated to be capable of being substitutable at the pharmacy without the need for intervention of a physician.
- There is no defensible basis for different Non-Proprietary Names other than to restrict competition
- Like State Substitution Restrictions, the effort to seek distinct non-proprietary names is primarily a commercial effort to make biosimilars and interchangeable products appear different to physicians and patients
- If successful, it will impair investment, innovation and the competitive savings expected from biosimilars and interchangeable biologics

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“Biosimilar” or “Biodifferent”? The Real Purpose of the Naming Proposal...

In order to maximize benefits of the pathway, as policies and laws are developed and implemented, should we be emphasizing similarities or differences?



“Unlike generic medicines where the active ingredients are identical, **biosimilars are not likely to be identical to the originator biologic**. Biosimilar development requires significant expertise, infrastructure and investment to demonstrate **safety** and equivalent efficacy and to ensure **safe, reliable** supply of therapies for patients.”



Why is Patient Safety A Concern in the Biosimilars Debate?

“Safety is a priority for the development of all medicines, but biologics raise safety considerations above and beyond those of chemical drugs. This is because biologics are more structurally complex medicines than chemical drugs, and even slight changes in their manufacture can cause undetected changes in the biological composition of the product. These changes can in turn affect the safety and effectiveness of the product in patients. The EPREX example provides a further rationale for not considering a follow-on product to be interchangeable with an innovative product.”

 A screenshot of a Genentech website page. The top left features the Genentech logo. Below it, the word 'Biosimilars' is written in a large, bold font. The page includes a navigation menu with links for 'SCIENTISTS', 'MEDICAL PROFESSIONALS', 'PATIENTS', 'MEDIA', and 'GO'. The main content area discusses the term 'Biosimilars' and emphasizes patient safety.

Genentech
A Member of the Roche Group

SEARCH

SCIENTISTS MEDICAL PROFESSIONALS PATIENTS MEDIA GO

Home / Knowledge / Biosimilars

Biosimilars

The term biosimilar refers to products that are marketed after expiration of patents, which are claimed to have similar properties to existing biologic products. Due to the complexity of biologics, a product can only be made that is similar, but not identical.

With patient safety as a priority, Genentech believes that:

Patient Safety

We believe that because of the differences between biologics, challenging issues exist relating to the development, approval and marketing of biosimilar products. We further believe that patient safety must be of paramount consideration when evaluating these issues.

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EMA Initiated Education to Address Unfounded Concerns about Biosimilars

Biosimilars in rheumatology: the wind of change

Christian K Schneider

Correspondence to Dr C K Schneider, Danish Health and Medicines Authority, Medicines Assessment and Clinical Trials, Copenhagen 2300, Denmark, and Twincore Centre for Experimental and Clinical Infection Research, Hanover, Germany;chsc@dkma.dk

....no batch of any reference product is 'identical' to the previous one—'non-identity' is a normal feature of biotechnology that has to be controlled by tight specifications of critical product attributes, within current technical and scientific limitations (inherent variability). The 'art' for a biosimilar is to demonstrate that the biosimilar is as close as possible to its reference product in all relevant functional and structural aspects.

...What is often not mentioned is that originator mAbs/cepts have undergone changes after their approval—this is what regulators call the 'life cycle' of a medicine.

Ann Rheum Dis March 2013 Vol 72 No 3

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Pharmacovigilance Does not Justify Unique Names

- Safety Reporting is not dependent on Non-Proprietary Names
 - NDC Number and its bar code is used to track and record products at the pharmacy and is unique to the product and manufacturing batch
 - Manufacturer name is on the product
- Alleged Pharmacovigilance concerns relate to all Medicines and Pharmacovigilance Generally, not Biosimilars
 - If there is a problem, fix it for all medicines, not just biosimilars
 - The Innovative Medwatcher smartphone APP is available and should be re-launched
 - ePrescribing also records NDC number which is the most useful identifier

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Pharmacovigilance Does not Justify Unique Names

- Safety reporting could be impaired by balkanization of Non-Proprietary Names
- Rare signals across biosimilar products could be missed if brand and biosimilar product data is treated as unrelated and are used to differentiate products

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Pharmacovigilance Does not Justify Unique Names

- Brand Products that are sold Interchangeably and Have the Same Name Despite:
 - Product Drift
 - Manufacturing Changes
 - Is the quality issue really with products that are not thoroughly tested to assure they are biosimilar or interchangeable?
 - EPREX
 - Heparin
- Competing Brand Products Also share the same Non-Proprietary Name, E.g.,
 - Kogenate antihemophilic factor (Recombinant) vs. Recombinate antihemophilic factor (recombinant)
 - Xyntha antihemophilic factor (Recombinant) plasma/albumin-free) vs. Advate antihemophilic factor (Recombinant) plasma/albumin-free)
 - Avonex Interferon Beta-1A vs. Rebif Interferon Beta-1A

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Restricted Access Programs

- Biosimilarity and Interchangeability Testing requires access to Brand Comparator Products
- Restrictive Distribution Networks and REMs Programs are increasingly used to track and potentially prevent comparative testing of biosimilar products, Cf., Actelion
 - Restricted Access programs are used to monitor, prevent and delay competitive development
 - Vertical restrictions with distribution chain prevent or restrict the re-sale of product to biosimilar competitors
- FTC should confirm that it is unlawful to restrict or delay access to reference product for FDA regulated biosimilar testing

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Conclusion

- Biosimilar and Interchangeable Biologic policy should be driven and measured by how it:
 - Promotes Innovation and Attracts Investment
 - Addresses Patient Needs and Patient Safety
 - Avoids using the least innovative and most anti-competitive solutions to achieve these objectives
- The opposition to Biosimilar and Interchangeable Biologic Competition:
 - Motivates restrictions on substitution of Interchangeable Biologics; and
 - Undermines the attractiveness of investment in, and access to, safer, more affordable biologics
- The FTC should encourage the FDA or HHS to adopt a Preemption Policy to ensure State Substitution legislation is:
 - Consistent with the BPCI; and
 - Facilitates investment to promote the use of innovation to provide patient access to safe and affordable Interchangeable Biologics
- The FTC should oppose as anti-competitive, efforts to:
 - Require different non-proprietary names; and
 - Restrict access to reference product for biosimilarity and interchangeability testing.

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June 4, 2014

Congressman Fred Upton
Chairman, Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

Dear Chairman Upton:

Thank you for the opportunity to submit comments on the 21st Century Cures Initiative. Health IT Now (HITN, www.healthitnow.org) is a diverse coalition of health care providers, patient advocates, consumers, employers and payers who support the adoption and use of health IT to improve health care and to lower costs.

We are convinced technology must play a foundational role in fostering 21st Century cures. Many aspects of our current health care system encourage inefficiency and promote waste aided and abetted by program and data silos. In some instances, federal policy and taxpayer dollars subsidize this waste. Perhaps worse, current technology solutions and data are not being brought to bear on pressing health problems. We thus believe the Committee has substantial opportunities to both address current problems and build a federal framework to encourage the discovery, development and delivery cycle. Our thoughts are outlined below.

- **Regulatory Framework.** We encourage Congress to establish a clear regulatory structure for health information technologies that can flexibly and nimbly keep up with the pace of technology innovation. We do not believe the current framework works well. For example, clear lines of jurisdiction are not well established, and expertise, staff and financial resources are not available in any current agency to ensure products can be determined safe and effective. We encourage the Committee to explore legislative solutions to build a new regulatory framework that is flexible, risk-based, and that lowers costs and eliminates duplicative regulatory efforts. We note that legislation has been introduced in the House and Senate to address these issues and that it would positively impact the entire discovery, development and delivery process.
- **Telemedicine.** In the past decade, the practice of medicine has changed dramatically. The convergence of medical advances, health information technology, and a nation-wide broadband network is transforming the delivery of care by bringing the health care provider and patient together virtually. By removing barriers such as distance, mobility, geographic, and time constraints, establishing common standards for technology enabled care delivery, and reforming licensure and payment models, telehealth has the ability to transform health care delivery by improving patient access to quality care while at the same time reducing costs and enhancing physician job satisfaction. Several key barriers, including interstate licensure, must be removed in order for physicians to maximize this technology. Changes in this area would positively impact the delivery process.

- **Discovery and Development.** Technology, including EHRs, Health Information Exchanges and mobile medical apps, is able to securely capture clinical and administrative information to create a vast data pool that can be used for genomics, population health and disease management, and clinical research. Unfortunately, the potential use of these vast data resources remain unemployed.

For example, EHRs can analyze and evaluate patient data instantly to determine eligibility for a clinical trial without ever compromising an individual's privacy. By requiring that clinical trial opportunities posted on ClinicalTrials.gov include pretrial screening information using standardized technical vocabularies, EHR systems will be able to compare relevant trial requirements to a patient's clinical and claims data without exposing the patient's private information. EHRs can enable clinical decision support functionality when a patient exhibits certain diagnostic factors that match pre-trial eligibility requirements for relevant clinical trial opportunities. By examining clinical indicators for potential participation in research, providers will be able to easily identify, as well as provide information on, relevant trials that may be beneficial to an individual's care. Patients and doctors could then decide whether participation in a trial makes sense for them.

Federal policy, notably current Meaningful Use program standards and data field standards in ClinicalTrials.gov, do not support this type of patient matching despite the clear benefit to discovery and development of new treatments and cures. We encourage the Committee to explore these opportunities and their potential applications to genomics, population health management and clinical trials. Changes in this area would positively impact the entire discovery, development and delivery process.

We appreciate the opportunity to share our initial thoughts with you on these issues and your dedication and commitment to ensuring the discovery, development, and delivery of innovative health care products and services. We have more information and analysis on the three areas described in this letter and look forward to working with you as you pursue the 21st Century Cures initiative.

Sincerely,



Joel C. White
Executive Director