Biotechnology Industry Organization

June 1, 2014

The Honorable Fred Upton
The Honorable Diana DeGette
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

The Biotechnology Industry Organization (BIO) thanks you for the opportunity to provide our initial thoughts regarding the Energy and Commerce Committee's ambitious and timely 21st Century Cures initiative. BIO is the world's largest trade association representing more than 1,000 biotechnology companies, academic institutions, state biotechnology centers, and related organizations across the United States. Entrepreneurial biotechnology companies are at the forefront of a revolution in our understanding of the genetic and biomolecular basis of disease, and these researchers are committed to developing the next generation of modern medicines to transform patient care. However, this goal can only be realized in an environment of forward-looking public policies that sustain scientific discovery and promote biomedical advancement. We are excited to work with you as you seek ways to keep our nation the innovation capital of the world. We focus here on the Committee's initial Call to Action paper, and we look forward to engaging with you on these and additional ideas to enhance medical innovation.

Your 21st Century Cures paper characterizes the drug development process as a cycle (a "learning healthcare system") in which understandings from each part of the cycle discovery, development, and delivery—informs the others. This approach advances biomedical innovation and enhances patient access to new medical products.

The traditional "linear" model of drug development is akin to running a marathon. When the race begins, a large number of drug candidates set out at the starting line (discovery). During the long and arduous race, a significant number of candidates drop out (development). Even toward the end, after expending tremendous resources, many are unable to complete the race. Only a few finish the race successfully (delivery). Similarly, medical product development, with its long timelines, large resource commitments, and high chance of failure, is risky for investors, inefficient for drug developers, and frustrating for patients and their families.

Instead, drug development advances best as a continuous, cyclical process similar to a team relay race on a circular track. By leveraging advances in genomics and our molecular understanding of disease, basic scientific discovery can help to put more drug candidates on the track to complete the race successfully. The development phase should advance regulatory science and utilize the latest drug development and clinical trial methodologies to speed and streamline the evaluation of each therapy's benefits and risks as the candidate rounds the corner of the track. Much like a relay, the

1201 Maryland Avenue SW
Suite 900
Washington DC 20024
202.962.9200 P
202.488.6306 F
bio.org

momentum carrying the candidate over the finish line and into the delivery phase can be harnessed to help inform research, as it powers the next candidate into the race. This collaborative, cyclical process can help ensure that more safe and effective therapies and vaccines reach patients in a timely manner.

The questions are how to be more aggressive in placing potentially successful ideas at the starting line, how to speed the translation of these ideas into important medical products as they move through the race, how to learn from the delivery of healthcare to inform the next lap of the development cycle, how to leverage partnerships and collaborations in a team approach, and how to maintain or create new incentives for innovation.

It is imperative that we find new solutions. This can be accomplished only if we continue to invest in scientific research, encourage the development and adoption of more efficient approaches to drug development, support collaborations and partnerships in the research and development endeavor, empower regulatory agencies to keep pace with science, promote the effective transfer of new technology, establish and defend policies that protect intellectual property, and promote reimbursement policies that ensure continued innovation and access to medicines for patients. A forward-thinking innovation ecosystem will ensure that patients continue to receive the benefits of new therapies and new cures as we move further into the 21st Century.

The Committee has asked how to incentivize, leverage, and harness our nation's abilities to develop new solutions to our most pressing health care needs. The following comments offer recommendations and ideas to advance that goal, but this should not be considered an exhaustive list of all the possibilities.

I. DISCOVERY

A. NIH Funding for Basic Research: Key to the Next Generation of Biomedical Discovery

The Committee's white paper identifies the importance of federal funding of the basic research that begins and underpins the process of discovery. The importance of having a sustained commitment to funding basic research cannot be overstated. Congress must focus on how to increase the NIH budget appropriately on an annual basis. Without such an annual increase, the budget and NIH's ability to fund meritorious research effectively and at a level that advances innovation declines with the inevitable increases in the cost of research. Furthermore, efficiencies in NIH processes could lead to cost savings.

Consideration also could be given to how public-private partnerships might help. Increasing private funding for government-sponsored basic and applied research would require discussion of how to incentivize such funding and how such funding would be administered. It would be important, for any such funding from for-profit sources, to determine how a system could be structured to prevent either the appearance of or actual conflict of interest.

B. Training and Retraining our Future Scientists

A key component to advancing discovery is research training, including training in regulatory science, and providing incentives that will encourage scientists to obtain and remain in government, academic, or private sector research and regulatory science positions in this country. For example, programs of the agencies of the Public Health Service, including NIH and the Health Resources and Services Administration (HRSA), as well as the FDA-funded Centers of Excellence in Regulatory Science and Innovation (CERSI) at the University of Maryland, could be examined for additional ways to provide research training and incentivize pursuit of careers in drug discovery and development research and as regulatory scientists at the FDA.

Additionally, we must have access to the most competitive graduate scientific talent. It is imperative that graduates are retained in the US upon graduation and accessible by government agencies and industry R&D departments. It is also important to ensure that companies engaged in significant drug development programs not lose essential talent during those programs due to the expiration of temporary visas. Retaining both domestic and foreign talent will enable American taxpayers to reap the benefits of funding top-notch American graduate education in the biological sciences, which attracts applicants from around the world.

C. Public-Private Partnerships: Incentivizing Pre-Competitive Collaborations: A Key to Addressing Scientific Barriers to Drug Discovery

Partnerships and enhanced communication, including pre-competitive information sharing, among NIH, FDA, academia, and industry, as well as partnerships among medical product developers, will yield enormous benefits. Today, several such public-private partnerships are working to find solutions to scientific barriers to understanding the underlying causes of diseases and to identify more efficiently and effectively valid drug targets and other tools and methods that could advance how we develop medicines. Examples are NIH's Accelerating Medicines Partnership (AMP), the Critical Path Institute, and the Biomarkers Consortium.[1]

It will be worthwhile to examine these collaborations to determine what drove them, what best practices may already be emerging, and what incentives would serve to expand the development of such partnerships. Enhancements such as safe harbors relative to intellectual property, added tax incentives, and mechanisms to address anti-trust concerns could be explored. It also could be informative to explore the possibility of making available, in a format that could inform future development, information derived from publicly funded discovery or private-public partnership development efforts that failed. If results from failed experiments are not published in peer-reviewed journals, providing such information by other means may be as informative as providing

[1] Other types of partnerships have also been successful. Several biopharmaceutical companies have also entered into collaborations with universities and academic centers, such as GlaxoSmithKline (GSK) and Yale University's drug discovery research collaboration to design a potential new class of medicines that degrade disease-causing proteins, and partnerships across industry, such as TransCelerate BioPharma.

results from experiments that succeed. In addition, discovery and development may be shortened and costs could be reduced by avoiding duplication of unsuccessful research efforts.

It would be informative and useful to conduct a comprehensive review of current research collaborations and identify what areas are being pursued and what areas need to be pursued. This type of activity should be done in collaboration with academia, patient advocacy organizations, and the biopharmaceutical industry. An important example is Alzheimer's disease. Without a clear focus on how to intervene, this disease alone will consume the health care system. Consideration should be given to a public-private mechanism beyond, but including, the existing AMP. This partnership could discuss the feasibility of and conduct a large-scale longitudinal study to identify the precursor and early signs of disease or disease risk. This information could be made publicly available so drug and device developers would have defined targets and potentially could develop ways to prevent and/or treat the disease. This would be done as a component of the existing National Plan to Address Alzheimer's Disease.

D. Setting Translational Research Priorities

As mentioned in BIO's May 20th testimony, BIO has been working with NIH's National Center for Advancing Translational Science (NCATS). For NCATS to achieve its goal to enhance the development of innovative medicines, it must engage in substantive partnerships and collaborations with industry, regulators, principal investigators, life science investors, and patient organizations. BIO has provided NCATS with recommendations for research priorities identified by the biopharmaceutical industry as areas that would best serve to improve the drug development process. Later in this document we will discuss further the importance of ensuring NCATS discoveries are adopted by the industry and accepted by regulators.

II. DEVELOPMENT

A. Clinical Trial Modernization: Reversing the Trends of Increased Timelines, Trial Sizes, Failure Rates, and Costs of Conducting Clinical Trials

Clinical trials have become larger, more complex, and significantly more expensive over the years. Clearly, there are multiple factors contributing to this, which may include the complexity of products being developed and increasing regulatory requirements.

Confronting the problem of increasing cost and duration of clinical trials is a daunting task. The biotechnology industry is committed to partnering with Congress, FDA, NIH, patients, academia, and other stakeholders to make meaningful progress toward improving the conduct of clinical trials. More efficient clinical trials translate to reduced barriers to market for innovative, safe and effective medicines, the ultimate goal of patients and industry. With this goal in mind, BIO launched its Clinical Trial Modernization Initiative (CTMI) in 2012, based on the pillars of four initial priority issues,

which we recommend to the Committee for consideration as part of the 21st Century Cures initiative. In the spirit of collaboration, BIO is also collaborating with key public-private partnerships to modernize the clinical development enterprise, including the Clinical Trials Transformation Initiative (CTTI), the Critical Path Institute, and the Biomarkers Consortium.

i. Use of Centralized Institutional Review Boards (IRBs)

Multicenter clinical trial protocols are most often subject to review by multiple, independent IRBs, which results in delays to study start-up and inconsistencies in the quality and conduct of ethical review. Centralized IRBs (cIRBs) promote greater efficiency, consistency, and quality of ethical oversight for multicenter clinical trials.

ii. Improving the FDA Qualification Process for Drug Development Tools

Drug Development Tools (DDTs), including biomarkers, patient reported outcome tools, and novel clinical trial designs, have the potential to improve public health and yield major impacts on the efficiency of drug development programs and their regulatory review. Despite this enormous potential, and a commensurate expenditure of resources, very few DDTs have been successfully qualified. Increasing the efficiency of the FDA qualification process for DDTs could greatly benefit the innovation ecosystem, enabling life-saving therapies to be delivered to patients more expeditiously.

Biomarker qualification is time-consuming, costly, and sometimes a dead-end. Again, a team approach, incorporating the basic scientific and medical knowledge of NIH; FDA's understanding, from broad and long experience, of clinical outcomes; and industry's expertise in drug discovery and development would be extraordinarily helpful. Together, NIH, FDA, and industry should develop consensus evidentiary standards rooted in shared scientific expertise and fundamentals to the qualification of biomarkers, both without regard to the therapeutic area and for particular therapeutic areas. Similarly, such an approach can be applied to the development of patient reported outcome measures and other types of drug development tools and study endpoints. BIO welcomes the opportunity to work with the committee to move the biomarker qualification process forward.

FDA reviewers should be encouraged to embrace the regulatory flexibility embodied by the Food, Drug, and Cosmetics Act to accept novel clinical trial designs and endpoints, and where appropriate to approve a drug based on a single trial and confirmatory evidence, as is often the practice in the context of rare disease drug development. For example, the *Food and Drug Administration Safety and Innovation Act of 2012* (FDASIA) provided FDA with greater flexibility to accept both surrogate endpoints and intermediate clinical endpoints that can be measured earlier in development for the basis of Accelerated Approval.

iii. Promotion of Clinical Trial Networks and Partnerships

Traditionally, in the United States and globally, there has been no established, enduring clinical trials infrastructure. This leads to considerable unnecessary cost related to study

start-up, enrollment, investigator training, and site certification. Advancing efforts by patient advocacy networks, medical centers, health care providers, and other stakeholders to develop clinical trial networks and collaborative partnerships could result in greater efficiency, consistency, and quality in the conduct of clinical research and improve the feasibility of clinical trials for special populations. For example, BIO has strongly supported the establishment of a global pediatric clinical trials network and has, in fact, actively convened stakeholders from industry, FDA, NIH, academic medicine, and others to discuss opportunities and challenges related to the potential formation a pediatric clinical trial network.

Research and clinical trials networks already exist, such as the Cancer Cooperative Groups funded by the National Cancer Institute and the Clinical Studies Network established this year by the Biomedical Advanced Research and Development Authority (BARDA) within HHS to advance medical countermeasures. The experience of, and learnings from, these groups can inform deliberations about the establishment of such clinical trial networks focused on other therapeutic areas. Legislation could authorize the establishment of such groups, with consultation between NIH and FDA, and with funding either from government sources, public-private partnerships, or on a fee-for-service basis. The application of data analytics to clinical trial networks also could help aggregate network and study site infrastructure, expertise, and participating patient populations into readily accessible databases, thereby allowing study sponsors to identify more easily the appropriate clinical network to run a particular trial.

iv. Risk-Based Approaches to Clinical Trial Monitoring

For many pharmaceutical and biotechnology companies, the predominant mechanism to monitor the progress of clinical investigations involves frequent visits to each clinical investigator site to evaluate study conduct and review data for each enrolled subject. Implementation of a risk-based approach to clinical trial monitoring that leverages centralized data monitoring through electronic data capture systems can lead to significant efficiencies for clinical trial sponsors. Particularly, BIO supports the work to develop standards for risk-based monitoring undertaken by TransCelerate BioPharma, a virtual, nonprofit organization comprised of representatives from nearly twenty leading biopharmaceutical companies with the mission to improve the overall quality and efficiency of clinical research using a collaborative, precompetitive approach.

Several specific suggestions for addressing the need to modernize clinical trials merit further analysis, such as the use of master protocols and "virtual" trials in which patients and physicians may participate remote from a trial site through the use of smart-phone and other technology. Expression of Congressional interest in more creative approaches such as these would help to advance them.

BIO is driving change in these priority issue areas by facilitating industry adoption of best practices, creating strategic partnerships, and advocating for policies to reduce regulatory barriers. We welcome the chance to work with the Committee to advance progress on these important initiatives.

B. Adoption of Modern Clinical Trial Designs, Tools, and Methodologies

Clinical trial design is challenging, and especially so for emerging companies. This is particularly true for therapeutic areas where the disease is poorly understood and endpoints are unclear. The utilization of novel endpoints also remains a significant regulatory challenge. For example, while there are numerous examples where non-traditional clinical trial design has been employed and novel endpoints have been used, the basis for that flexibility is poorly understood and decision-making is inconsistent across FDA review divisions.

There is also significant interest in using adaptive design trials in combination with Bayesian methods to accelerate clinical development. These novel trial designs can allow sponsors to make better decisions more efficiently, decrease development time, and maximize trial resources. Improving the acceptability of adaptive trials will enable faster and cheaper clinical trials while maintaining the same standards of quality. It is important to consider how standards for flexible clinical trial design and novel endpoints could be developed and applied consistently.

It would be helpful for Congress to encourage or specifically authorize FDA to accept data from non-traditional sources, which may include historical data, data from electronic health records, claims databases, registries, or other sources.

Technology utilization in health care continues to advance at a rapid rate. Patients currently use devices, apps, and the internet more than ever to research and monitor their health. FDA standards of how to utilize these new tools in clinical trials has not kept up with marketplace innovation. The manner in which patients are caring for their diseases and generating data is changing rapidly and there are no clear rules for sponsors for how this translates into the applied use in clinical research. Current regulations limit the ability of sponsors to validate such data sources/repositories. Guidance from the Agency on how to use patient (or investigator)-focused tools in clinical research would be extremely beneficial in fostering innovation. Clarification is needed on the types of data measured, collection and validation methods, and expectations of collection devices that help accelerate adoption of innovation into research. In addition, guidance on sponsor-to-patient engagement models in clinical trials (e.g., clinical trial design website for robust patient understanding before they visit investigator sites) will help accelerate patient engagement in research.

As the Committee considers various approaches to trial design and how Congress can best encourage FDA to take account of new ways of doing trials, we also suggest an evaluation of the traditional 3-phase trial approach. Under what circumstances, for example, can the approval of a medicine be based on data and information from two clinical trial "phases," with confirmatory evidence and additional information collected post-approval?

Finally, there are numerous public-private partnerships and governmental agencies working on modern approaches to drug development. They include the Biomarkers Consortium, the Critical Path Institute, the Clinical Trials Transformation Initiative, and the Reagan-Udall Foundation. However, there is no clear path where findings or

discoveries by these entities are evaluated and adopted (when appropriate) by FDA. This can lead to hesitancy by industry to fund or utilize modern tools and approaches. BIO looks forward to working with the Committee to identify solutions to this problem.

C. Improving Scientific Dialogue During Drug Development

BIO continues to discuss how to improve scientific dialogue between industry and FDA throughout drug development. We welcome the opportunity to work with Congress and FDA to improve these types of communications. Additionally, BIO has identified the ability to access external experts and incorporation of patient perspectives as crucial to ensuring that the drug development and review process take into account both current medical science and patient needs.

Congress responded to this concern with Section 903 of FDASIA, which outlines a process for consultation of external experts on rare diseases and targeted therapies and on genetic targeting of treatments. For medical countermeasures—drugs, vaccines and diagnostics that help protect against bioterrorist threats, pandemic influenza, and other emerging infectious diseases—Congress authorized FDA's use of regulatory management plans (RMPs) to facilitate formal scientific discourse during various stages of product development and review. It may be worthwhile to examine the progress of these programs and how they might be expanded to other types of products.

D. Expediting Development of Innovative Therapies

We appreciate the committee's commitment to accelerating drug development through the enactment of expedited development programs under FDASIA, including Breakthrough Therapy Designation and modernized Accelerated Approval. BIO looks forward to discussing these programs further and evaluating how other potential mechanisms can complement these programs or fill gaps in the existing armamentarium of regulatory programs.

The Committee's questions regarding wider acceptance of flexible clinical trial designs aided by innovative technologies are timely and reflective of conversations among stakeholders as we work to advance personalized medicine.

- The Committee could evaluate such proposals as adaptive clinical trial design, I-SPY trials, and utilization of diagnostics and biomarkers to identify subpopulations, to determine whether and how best to authorize FDA to move forward with such approaches as appropriate.

- The European Medicines Agency recently launched an adaptive licensing program, also referred to as progressive licensing. Similar to the Special Medical Use (SMU) concept that has been discussed in Congress, PCAST, and elsewhere, the process would begin with authorization for use of a medicine for a small population or subpopulation and build stepwise toward a "full" market authorization with the collection of additional evidence. The Committee could consider these European concepts, or may wish to re-consider the previously proposed SMU pathway, by which FDA could approve a product, at the sponsor's request, for a limited subset

of the population affected by a particular condition. The product label would inform health care providers, patients, and caregivers that the product has not been demonstrated to be safe and effective outside the specific subpopulation. The Committee may wish to make clear that such mechanisms meet FDA's substantial evidence standard for the purposes of approval and should be reimbursed as such

- Finally, the Committee also has raised the question of a possible different approach to the approval process for supplemental indications, as discussed in Section IIIA.

BIO welcomes the opportunity to work with Congress, FDA, patients, and other stakeholders in exploring these types of proposals. Such analysis will help in the development of a regulatory system that looks at new ways of collecting data and novel data sources, that encourages flexibility to advance the development of the best medicine for each patient, and that takes into account the needs of patients in the context of the disease being treated.

Advancement of personalized medicine will rely heavily on the development of diagnostic tools that can be used to identify patients most likely to benefit from specific medicines, or less susceptible to certain adverse effects. The development of such tools, and of companion diagnostics and combination products, can be slowed or hindered unless there is improved coordination and cooperation among CDER, CBER, and CDRH. Such mechanisms as joint timelines could be explored as a way to ensure process improvements.

E. Incentives for Innovation

The concept of regulatory exclusivity has long been recognized as one that advances innovation and promotes, as in the case of orphan drug market exclusivity, the development of medicines—or new indications for existing medicines—that otherwise might not be developed. BIO encourages the Committee to look at various approaches to intellectual property incentives, including through refining both patent and data protection, to determine if the current structure continues to promote innovation in the best way possible.

Consideration also could be given to the establishment of incentives for the development of interventions for serious diseases that pose significant public health issues, such as Alzheimer's disease and multi-drug resistant organisms. These incentives could take the form of regulatory exclusivity, patent protection, or other approaches.

F. Management Tools

Updated management methods could be considered—achievable either legislatively or administratively but with Congressional approbation—that could assist the Agency to adopt new approaches to review, including the evaluation and adoption of new medicines development tools. For example, routine third party evaluation of FDA processes and progress might be a successful approach. Such reviews might consider

matters including the consistency, predictability, and transparency of decisions across review divisions; management, training, and oversight of new FDA review staff, including direct interaction between more- and less-experienced review staff, to promote regulatory best practices; and adoption of innovative tools, techniques, and analytics for clinical trials results.

A new FDA Management Review Board composed of outside experts could, on a periodic basis and at the request of the FDA Commissioner, provide fresh and independent thinking.

The Agency could be encouraged to consider a quality management system for each Center that could explicitly define, measure, analyze, improve, control, and validate key processes utilized by its scientists as decisions are made.

A new FDA Chief Innovation Officer might help advance the transparent evaluation and integration of innovative tools and approaches in FDA review processes and also could serve as an external link between FDA and work being done by the private sector, other government agencies (such as NCATS), and public-private partnerships. Such a connection could advance the evaluation and acceptance of new methodologies and approaches and might, in particular, ensure early evaluation and expeditious acceptance of NCATS findings that could improve the drug development process.

G. Rare Disease Therapies

For patients living with rare diseases and conditions, the Orphan Drug Act changed the face of discovery and development. The Act spurred not only the development of new treatments for those diseases, but also the creation of an entire industry that specializes in the discovery, development, and delivery of drugs and biologics for rare diseases. Prior to its enactment in 1983, only 38 drugs were approved in the United States specifically to treat orphan diseases. Since 1983, the FDA has approved more than 350 orphan drugs and granted orphan designations to over 2,000 compounds. The Orphan Drug Act has clearly accelerated the type of innovation that the Committee is trying to encourage and it could serve as a model for future legislation in this area.

Orphan drug manufacturers are often small or mid-sized companies that rely on the Act's provisions to remain viable. In particular, the orphan drug tax credit has offset some of the costs of developing drugs for small patient populations by allowing companies to develop products that otherwise would not be commercially feasible. One important way to spur continued innovation in the rare disease space is to protect and preserve the Orphan Drug Act, including the orphan drug tax credit, to allow these companies to continue to innovate and to attract new entrants into the industry. This will ensure that new life-saving products continue to be developed for the 30 million Americans who live with rare diseases.

In terms of accelerating innovation, another important topic for orphan drug manufacturers is the flexibility of the FDA's approval process. The Committee rightly raises the issues of validated biomarkers and surrogate endpoints—topics that take on new importance when the US patient population can comprise fewer than 100 people in

some rare diseases. Rare disease drug manufacturers face unique challenges in clinical trial design and drug approval and appreciate the Committee's acknowledgement that efficient trials with flexible designs should no longer be the exception to the rule. FDA flexibility in other areas, such as non-clinical requirements and certain manufacturing requirements (for example, flexibility regarding the number of clinical-scale and commercial-scale validation batches), is also essential to the success of orphan product development.

A key component of drug development in rare diseases is engaging the patient community early on in clinical development of new therapies, to ensure the patient's perspective is considered. This supports the development of patient-centric clinical protocols and optimizes enrollment as well as patient compliance and retention. Ultimately, patient input may accelerate the approval of new treatments.

H. FDA Funding

Investment by biotechnology firms and venture capitalists is predicated on working within an FDA regulatory framework that is predictable, consistent, and well-resourced, and that has the scientific capability necessary to evaluate the benefits and risks of novel products in a timely manner. An effective, efficient, and well-funded FDA is critical to encourage biomedical innovation to deliver treatments and cures. We urge Congress to consider FDA's critical role in the innovation ecosystem and to provide ample resources as part of the annual appropriations process.

In addition, BIO strongly supports legislation that would prevent user fees from being sequestered in the future sequestration, as this would threaten FDA's ability to ensure patients get new treatments and cures at the earliest possible time.

III. DELIVERY

A. Post-Market Real-World Data

Advancements in information technology and the adoption of electronic health records place biomedical sciences at the cusp of fully realizing a "learning healthcare system." Such a system can evaluate real-world data to assess the safety and efficacy of medical interventions, including drugs and biologics, to support the cycle of biomedical innovation from drug discovery and development to the point of healthcare decision-making.

Continued technological advances in gathering and employing data have the potential to improve the timeliness of drug development without impacting high standards for quality and safety. For example, while randomized, controlled clinical trials (RCTs) are considered to be the gold standard to assess safety and clinical efficacy, they often evaluate uniform populations remotely connected to the use of drugs in regular clinical practice or in settings reflecting real-world health care delivery. RCTs can readily identify higher-frequency adverse events and assess clinical efficacy, but they must enroll

thousands of patients to be powered sufficiently to detect rare adverse events or slowly progressing clinical manifestations. Yet increasing the size, length, and complexity of clinical trials is not an economically sustainable option and places further burdens on the ability of researchers to enroll and conduct clinical trials feasibly.

Rather, we should pursue approaches that more closely integrate reasonably sized pre-market clinical studies and real-world data with mandatory post-market surveillance and analysis of additional real-world data to assess safety and efficacy further and to refine the therapy's benefit/risk profile. For example, marketing approval should be granted on the basis of a demonstration of safety and efficacy in a highly targeted patient population (that would require fewer patients in clinical trials) with analysis of electronic health record data and "virtual" clinical studies in a post-market setting to support expanded indications.

As part of the Agency's Sentinel Network initiative, FDA has made considerable progress in developing the tools and methodologies for assessing post-market data to identify safety signals; we should continue to build upon that foundation to also consider efficacy endpoints. While the scientific methods in this area continue to evolve—and are evolving in particular through the Reagan-Udall Foundation's Innovation in Medical Evidence Development and Surveillance (IMEDS) program—we must embrace a future where FDA and industry can be aligned to better leverage real-world data to answer key research questions more efficiently than in large-RCTs.

Enabling the appropriate use of rapidly growing digital health information can help not only to inform regulatory approval and fulfilling post-approval commitments, but also in providing relevant information at the point of healthcare decision-making. Crucial to this effort will be broadening access to existing federal data resources—such as from Centers for Medicare and Medicaid Services (CMS)-administered federal healthcare programs, NIH, and the Centers for Disease Control and Prevention—and standardizing the collection of these data across various sites of care to provide a comprehensive, continuous picture of an individual's health and the care he/she receives.

B. Pharmacoeconomic Data and Other Information

Current law deals with the important question of providing payers and others with meaningful information regarding the pharmacoeconomic benefits of medicines. However, implementation of Section 114 of the *Food and Drug Administration Modernization Act of 1997* (FDAMA) has undermined innovators' ability to meet requests for such information. The committee could evaluate how this important provision could be implemented in a less restrictive way to allow manufacturers to discuss more fully the value to the healthcare system of their innovations.

More broadly, provision of other truthful and non-misleading information to providers, payers, and patients also should not be impeded by unnecessary and cumbersome regulatory restrictions or requirements. Such approaches hinder users of medicines from accessing information that can help them use the medicines most effectively.

C. Predictable and Transparent Payment and Coverage Policies

While improvements in the discovery and development of medical products are critically important in the bench-to-bedside continuum, patients must be able to access the products or those improvements will be meaningless to them. Predictable and transparent payment and coverage policies that foster innovation are critical to ensuring that treatments and cures get to the patients who need them most.

As a representative of an industry committed to discovering new cures and ensuring patient access to them, BIO closely monitors changes to how our members' products are covered and reimbursed. Policies that limit access to novel medical therapies and technologies can lead to potential delays in obtaining care, or sub-optimal care, ultimately resulting in higher health costs and poor health outcomes. Conversely, innovations such as new medical therapies can reduce the burden of, or even cure, costly diseases, as well as keep total societal costs down. Yet, increasingly we hear from those private investors funding our smallest companies that reimbursement uncertainty is forcing them to look to alternative investments—not just different companies, but different, unrelated industries altogether. Thus, we ask that throughout your evaluation of payment and coverage policies, the Committee consider the important role market-based policies have in incentivizing biopharmaceutical innovation and their potential to constrain costs and improve overall access (e.g., Medicare Part D).

While Congress and FDA have spent considerable time removing barriers to innovation from the drug review process, CMS is often skeptical of new, innovative therapies, focusing solely on cost considerations rather than on potential patient benefit. Moreover, CMS has pursued policies that have served to decrease predictability in the coverage process. One example is CMS's use of Coverage with Evidence Development (CED) as an outcome of the National Coverage Determination process. CED offers the specter of coverage, but actually limits patient access to innovative technologies by requiring manufacturers to conduct, and patients to enroll in, post-approval studies—distinct from any FDA-required post-market monitoring—before coverage is granted. Because private payers often follow CMS's coverage and payment decisions, it is all the more important for this Agency to promote responsible benefit design that better recognizes truly innovative products early. CMS should also work with product sponsors as soon as possible to resolve any coverage and payment issues to ensure patient access to the care—which includes the therapies as well as the healthcare providers—that they need. As we previously noted, lack of clarity from CMS creates uncertainty for companies and their investors, limiting investment. Thus, the Committee should consider how existing and proposed policies across the Department of Health and Human Services serve to create predictability in the coverage, coding, and reimbursement processes and whether they focus on sustaining incentives for innovation over the long term.

There are actions the Committee may consider in addition to CMS's coverage policies that would facilitate getting novel treatments and cures to patients in a timely manner. For example, CMS has established a process for assigning payment codes to new drugs and biologics. This process can take more than a year after the FDA approval of a new drug or biologic to assign a code because CMS only convenes the advisory panel once

per year. The Committee could direct CMS to assign payment codes more frequently during the year, which would improve payment and data accuracy for new products.

Another area for Committee evaluation is whether the payment mechanisms for accommodating new interventions within existing bundled payment systems (i.e., for new technology add-on payments, pass-through status) are sufficiently furthering the aim of promoting access to, and incentivizing, innovative technologies. Similarly, the Committee may choose to examine Accountable Care Organizations and other novel care delivery systems to assess the mechanisms in place or needed mechanisms to encourage the appropriate adoption of innovative drugs and biologics by participating providers.

The Committee also should consider evaluating patients' out-of-pocket costs and the impact on access to innovative therapies. This examination could be part of a broader evaluation of the impact of high-cost sharing benefit design (e.g., specialty tier) across Federal and Exchange and across different patient populations (e.g., oncology patients, patients with rare diseases).

Finally, the Committee could evaluate the impact of other Federal programs and policies on innovators' ability to continue to develop the treatments and cures of tomorrow. To the extent programs are managed or implemented with the goals of achieving near-term cost savings, they may have the unintended consequence of chilling future innovations. This is especially true in the area of prevention, which offers huge societal benefits, but often is not incentivized by existing coverage and reimbursement policies. However, this is also true, for example, in the case of therapies to treat chronic diseases like obesity. Despite the mounting national obesity epidemic, payment for obesity therapies is not available in the Medicare program and the development pipeline in this space is not robust. Thus, not only does the policy of non-coverage limit today's patients from accessing effective treatments, but it may also limit the availability of treatment options for future generations of patients by disincentivizing research and development in this field. The potentially negative health outcomes of limited access and a diminished pipeline will likely be compounded because obesity is a comorbidity that can dramatically impact the effectiveness of care provided for other chronic conditions (e.g., cardiovascular disease, diabetes). This, in turn, can increase overall costs of care due to increased hospitalizations, surgical interventions, and physician office visits.

An analogous risk to sustaining longer-term biopharmaceutical innovation, and potentially more far-reaching in scope, is the tremendous growth of the 340B Drug Discount Program, particularly in the last few years. This unfettered growth may ultimately impact innovators' ability to continue reinvesting in their development pipelines. Additionally, growth in the 340B program has exacerbated long-standing concerns that the program's intent—to expand access to pharmaceuticals for uninsured, indigent populations—is not being fulfilled.

D. Principles for Payment System Redesign

BIO's primary goals are to ensure that patients have access to appropriate therapies and to protect the incentives needed to develop innovative medicines to treat the patients of

tomorrow. For example, BIO continues to support legislation that authorizes enhanced reimbursement for targeted, novel antibiotics and antifungal agents.

The principles that guide our work are the following:

- *Quality*: Protect high-quality care. Payment reform models must focus on the quality of care delivered, not narrowly on lowering the cost of care.

- *Patient Impact*: Any proposed payment-system reforms must integrate a "patient impact" assessment into their development.

- *Access*: Protect patient access to innovative biopharmaceutical therapies, drug delivery devices, diagnostics, and vaccines.

- *Adherence*: Support patient adherence to therapies.

- *Innovation*: Maintain incentives to develop innovative therapies to address patients' unmet needs and to discover the cures of tomorrow. The research and development of new cures and breakthrough therapies must be a high priority of our nation's health care system—a system that ideally pays for health, wellness, and innovation.

- *Evidence*: Ensure that sound evidence is used for payment policy changes.

- *Transparency*: Ensure sufficient stakeholder input through a transparent, predictable, and inclusive process.

- *Adequate Reimbursement*: New payment models should not be undertaken without comprehensive evidence that such changes will improve outcomes while lowering overall costs and must place central priority on ensuring access to quality patient care and improving outcomes. Issues involving reimbursement should be resolved during the development process, so as to avoid creating uncertainty for patients, product sponsors, and investors.

IV. ENCOURAGING INVESTMENT & MAINTAINING GLOBAL LEADERSHIP

As mentioned in BIO's May 20th testimony, we are facing unprecedented competition from around the globe to be the leader in biomedical research. In 2008, China pledged to invest $12 billion in drug development, and in 2011, the Chinese government named biotech one of seven industries that will receive $1.7 trillion in government funding. Europe is pumping $2.65 billion into the European Union's Innovative Medicines Initiative. While the US has developed more cures and innovative medicines than any other country and is home to over 2,500 biotech companies, this is not a position that will be sustained without continued investment and policies focused on supporting and incentivizing the next generation of biomedical discoveries, treatments, and cures.

As Congress continues to discuss reforming the corporate tax code, consideration should be given to promoting innovation through research and development and advanced

manufacturing. Current tax laws impede this country's ability to compete with other industrialized countries on the global stage. Since 1988, the average OECD corporate income tax rate (excluding the US) has dropped 19 percentage points, while the US Federal rate has increased by one percentage point. BIO urges Congress to reduce the corporate tax rate so that it is globally competitive for established companies.

It is equally important that Congress create new and adjust existing incentives and structures to enhance long-term private investments in innovation. To this end, BIO has been working with Congress for the past few years on legislative proposals that would bring in new investors and encourage more investment in high-reward, research-intensive industries including biotechnology. One of these proposals would reform the tax laws to allow small, research-intensive companies to enter into research project partnerships with investors that would allow losses and credits generated by the research project to pass through to the investor. This proposal would be a game changer for the industry and spur significant investment into private biotech companies that are working on medicines of tomorrow.

BIO looks forward to discussing this and other BIO tax proposals that would encourage investment and help ensure US global leadership in biomedical research and development.

Conclusion:

Modern biotechnology is helping to heal the world to combat debilitating and rare diseases, and advance patient care through precision medicine. The science of biotechnology isn't easy. Nature does not readily yield her secrets. Still, every day brilliant scientists and researchers decode a bit more of the language of life. The science continues to astonish and amaze. Today, there are more than 250 biotechnology health care products and vaccines available to patients, many for previously untreatable diseases. BIO strongly believes that advancements in our understanding of the molecular basis of disease will unleash a new era of modern medicine that will transform the standard of care for serious illnesses and chronic health threats across our nation and the world. However, this will only be possible if supported by sound, forward-looking public policies that promote biomedical science and break-down the barriers that impede American innovation.

The 21st Century Cures Initiative holds enormous promise to help realize the next generation of lifesaving medicines. Thank you for the opportunity to provide the input of the biotechnology industry and we look forward to continuing to work with the Committee and provide additional thoughts as the 21st Century Cures Initiative advances.

Comments of the Remote Cardiac Services Provider Group

Re: 21st Century Cures: A Call to Action

The Remote Cardiac Services Technology Group (RCSPG) strongly supports the Call to Action issued by Chairman Upton, Representative DeGette, and the House Energy and Commerce Committee. The RCSPG is a coalition of providers that furnish over half of the remote cardiac monitoring (RCM) services in this country. Many of our provider companies are also leaders in the development of medical devices used in RCM.

We strongly welcome the Call to Action because we are medical innovators whose primary mission is to allow patients to be monitored in their homes, rather than in more expensive hospital settings. We understand that the Initiative is focused on saving lives and advancing development and discovery. As the federal government is intimately involved in determining what services are available to Medicare beneficiaries and how those services are paid, we believe federal policy, including payment policy, should support the use of these services to optimize patient care proactively.

Unfortunately, efforts by RCM companies to provide patients with the most advanced technology are being stymied by outdated Medicare reimbursement based on an obsolete methodology where patient services were only provided in a physician office or a hospital. If we want 21st Century Cures we need a 21st Century payment system – one that recognizes the costs of IT infrastructure and telecommunications systems.

Medicare reimbursement for these cost-saving and life-saving services has declined precipitously in the last several years because Medicare payment policies do not recognize the substantial technology costs necessary to effectively furnish these services in the ambulatory setting. We believe this payment decline has, and will, decrease access to these important diagnostic services – services that allow patients to be monitored while being productive citizens in the home or at work and which provide physicians with essential information that allows them to effectively diagnose and treat complex arrhythmias.

If Medicare reimbursement continues to deteriorate and if new technologies are not appropriately priced, then innovation will be discouraged, patients will lose access, and physicians will be deprived of the tools they need to diagnose, and costs will increase as patients are shifted back to more expensive, in-hospital testing. For example, atrial fibrillation (AFib) increases the risk of stroke by 4-5 times and accounts for 15-20 percent of ischemic strokes – i.e., 120,000 to 160,000 strokes annually. Prompt diagnosis of AFib is critical in ensuring patients the appropriate treatment to prevent strokes from occurring. RCM technologies are the best tools for diagnosing

these conditions. RCM also saves the health system money by diagnosing AFib in a cost efficient manner outside the walls of the hospital and by diagnosing AFib for treatment before the expensive, debilitating stroke occurs. An inpatient admission for a stroke costs the healthcare system upwards of $20,000 – not to mention rehabilitation costs or the very real societal costs associated with long-term or permanent disability.

Government coverage of new RCM technologies must also keep up. There is little point in developing and refining these technologies if Medicare and other payers do not update their coverage policies even when a service is shown to be clinically superior and to lower costs over time. Savings that may accrue over years, including savings to individuals and society through reduced disability and longer participation in the work force, need to be considered in the development of coverage and payment policy. Even risk-sharing arrangements which reward providers for saving costs, a short-term view tends to prevail with savings measured on an annual or episode-of-care basis.

The RCSPG has called upon Congress to order a GAO study that would review the current reimbursement system for RCM and other remote monitoring and appropriate language is included in the SGR reform bill. This study is needed to help bring Medicare reimbursement into the 21st Century.

We appreciate the work the Committee has embarked on and look forward to making a meaningful contribution to this endeavor. If you have questions and for more information about the RCSPG, please contact Peggy Tighe, RCSPG representative, at [redacted] or [redacted]

August 11, 2014

The Honorable Fred Upton (R-MI)
Chairman
Committee on Energy and Commerce
U.S. House of Representatives
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Diana DeGette (D-CO)
Member
Committee on Energy and Commerce
U.S. House of Representatives
2368 Rayburn House Office Building
Washington, DC 20515

Dear Chairman Upton and Rep. DeGette:

On behalf of the National Venture Capital Association (NVCA) and our nearly 400 members, I want to thank you for your leadership on the issue of medical innovation and the launch of the 21st Century Cures initiative. We appreciate the judicious manner in which you are approaching this important reform effort. There is no simple solution to close the gap between the rapid advancement in the field of medical research and the many factors that hold back innovation in the development of innovative new medicines and medical devices. Your approach to listen first and then act will ensure this initiative is a success.

As you have acknowledged repeatedly throughout this process, it's not enough to simply look at one stage of the medical innovation arc; you need to examine the full arc—from discovery to development to delivery—to really get to the root of the issue. We believe that by taking a holistic look at each individual stage of the medical innovation process, you will ensure the greatest chance for success.

In many ways, the fate of the U.S. medical innovation ecosystem rests in your hands. If more is not done to improve the drug and device development process and modernize our regulatory and reimbursement systems to keep pace with the rapid advancement in medical research, the U.S. is at risk of losing its leadership in medical innovation.

NVCA believes it is critical to advance public policies that will encourage investment in medical innovation so new treatments and cures will be available to patients. Central to doing so is to continue to reform our regulatory system to make it agile and flexible to the changing pace of innovation as well as develop a predictable and transparent reimbursement system that pays for innovative medical products that provide value to patients and the overall healthcare system.

We appreciate your acknowledgement of the venture capital industry as an important stakeholder in this discussion and your understanding of the critical role venture capital plays in the advancement of medical innovation in the U.S. Over the last three decades, venture capital has been the primary force in translating scientific discoveries into medical advances for patients and remains one of the few sources of capital to fund and nurture small, emerging companies focused on medical innovation.

However, venture capital investment in early-stage life sciences companies has been facing significant pressure in recent years. In fact, in 2012 the number of first-time financings of new life sciences companies hit a 15 year low. A primary reason for this long-term decline in financing for medical innovation has been the increased time, cost and uncertainty involved in developing new drugs and medical devices. In 2013, early-stage venture financing of life sciences companies rebounded somewhat, although it remains well below the levels needed to keep pace with advances in science and medical research. An important reason for this recent rebound is the improved regulatory environment for innovative product development, which is related to the Food and Drug Administration Safety and Innovation Act of 2012. This highlights the critical role that this committee can play in advancing public policy initiatives that help encourage investment in medical innovation.

Regulatory and reimbursement policies have a major impact on the flow of private investment capital. Against this backdrop, the following are NVCA's high level recommendations on how to encourage investment in the innovative drugs and medical devices of the future. We look forward to working with you to develop specific and more granular concepts based on these recommendations.

Make medical innovation a national priority

- Create a national advocacy strategy focused on preserving U.S. leadership in medical innovation.

Continue to fund basic science and applied R&D

- Support continued government funding for basic research and development which drives the discovery of breakthrough innovations with the potential to cure disease and treat unmet patient needs.

Provide appropriate incentives for collaborative public/private partnerships that can help address key barriers to innovation

- Encourage and support continued FDA efforts to implement a patient-centered benefit/risk framework for drug and medical device development.

- Encourage the work of the Medical Device Innovation Consortium (MDIC) and other public-private collaborations to improve regulatory science and enhance drug and medical device development.

Develop novel, interactive and flexible regulatory models for disruptive innovation

- Ensure that the FDA has the resources and the mandate it needs to fulfill its dual missions of protecting patient safety and encouraging medical innovation.

- Continue to develop flexible and innovative regulatory pathways for cutting edge drugs and medical devices.

- Create new approval pathways, such as the proposed Special Medical Use pathway, that enable the development of drugs and medical devices for subpopulations of patients in areas of high unmet need.

- Review and ensure the effectiveness of FDA's Special Protocol Assessment (SPA) process.

- Support the use of innovative clinical trial designs, including the use of adaptive trials, biomarkers, and single-arm clinical trials with historical control groups under appropriate circumstances.

Provide greater clarity, transparency and flexibility in the regulatory process for laboratory developed tests (LDTs) to encourage investment and development of personalized medicine that will provide value to patients and the healthcare system

- Develop clarity, transparency and flexibility in the regulatory process for LDTs that will keep pace with scientific advances and genomic science.

- Organize a partnership between government and the private sector to align the common interest in advancing the improvement of patient care using precision or personalized medicine.

Provide greater transparency and use of clinical trial data

- Explore the opportunity to unleash the power of information by publicly releasing FDA submissions and correspondence between companies and FDA, with a mechanism to redact legitimate trade secret information. This will provide a heightened level of transparency that will allow better drug and device development decisions and more efficient clinical trials, and will help ensure that investment flows to the most promising areas of drug and device development.

- Facilitate innovators' access to post-market clinical data in patients' electronic health records.

Work to integrate real world data into the drug and medical device review process

- Achieve the appropriate balance of pre- and post-market data requirements for regulatory approval that encourage the development of innovative products.

Develop coverage and payment policies that reward investment in medical innovations that provide value both to patients and the healthcare system

- Develop a set of principles on how to evaluate the value of innovative medical technologies.

- Promote coding, coverage and payment policies that support innovations that can improve the cost, quality and outcomes of medical care.

Provide greater patent and intellectual property incentives for medical breakthroughs

- Extend data exclusivity period in areas of unmet need.

- Assure that efforts to reform the patent system to deal with "patent trolls" do not undermine the need of legitimate patent holders for protection of their intellectual property.

Summary

The success in the initiatives we have outlined above will help ensure that patients get access to innovative new treatments and cures, and will help cement U.S. leadership in medical innovation and generate economic growth and high-quality jobs across the U.S. for decades to come. We look forward to being part of the solution.

Sincerely,

Bobby Franklin
President & CEO

Cc: House Energy & Commerce Committee Members

AstraZeneca · 1800 Concord Pike · Wilmington, Delaware · 19850
T: 302-885-9009 · astrazeneca.com

August 12, 2014

By Electronic Delivery

The Honorable Fred Upton
The Honorable Diana DeGette
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

Dear Representatives Upton and DeGette,

On behalf of AstraZeneca, we are writing to express our support for the Energy and Commerce Committee's timely and important 21st Century Cures initiative and to submit our initial, formal comments to the Committee. AstraZeneca is a global, innovation-driven biopharmaceutical business that focuses on the discovery, development and commercialization of prescription medicines, primarily for the treatment of cardiovascular, metabolic, respiratory, inflammation, autoimmune, oncology, infection and neuroscience diseases.

The Committee rightly cast a wide net for input, answers, and feedback on its initiative. AstraZeneca is pleased to offer the following recommendations and ideas to advance the discovery, development, and delivery cycle. We are committed to working with the Committee in pursuit of its initiative and welcome the opportunity to discuss further details with the Committee.

Summary of Recommendations

- Ensure that NIH and other-science based agencies are well-funded on an annual basis.
- Vigorously support translational research.
- Look to existing initiatives (such as the Clinical Trials Transformation Initiative and the TransCelerate initiative) for innovative ideas to modernize the clinical trial ecosystem.
- Appropriately incentivize a healthy clinical research site landscape.
- Promote the development and regulatory acceptance of modern clinical trial designs, tools, and methodologies.
- Meaningfully incentivize personalized medicine.
- Encourage innovation across all therapeutic areas.
- Ensure payers, formulary committees, and similar entities have timely access to relevant information about medicines, particularly new medicines.
- Examine marketplace challenges and their impact on patient access to innovative medicines.
- Appropriately protect intellectual property.

Discovery

Sufficiently invest in basic biomedical research. Sustained, robust Federal funding for the National Institutes of Health (NIH) and other science-based agencies is critical to the future of scientific discovery and innovation. The basic research and effective industry-academic collaboration supported by these agencies lays the foundation of scientific and clinical knowledge for the next generation of treatments and cures.

Over the past 10 years, AstraZeneca has built robust strategic collaborations with NIH in disease areas of oncology, mental health, and cardiovascular. In oncology alone, AstraZeneca is engaged in more than 20 Cooperative Resesearch and Development Agreements (CRADAs), including the first industry clinical CRADA (2005), first super CRADA in industry, and the first Investigational New Drug (IND) transitioned to NCI (cediranib). These CRADAs have brought together the best scientists across industry, government, and academia and engaged over 75 NIH-funded collaborative and academic centers, reached 3100+ patients, and advanced development of more than ten novel/novel combinations of products.

AstraZeneca strongly recommends that the Committee ensure that NIH and other science-based agencies are well-funded on an annual basis.

Support translational research. The process of applying discoveries generated during research in the laboratory, and in preclinical studies, to the development of trials and studies in humans is often filled with many gaps. These gaps can lead to expensive failures and/or delays where the ultimate result is that new therapeutics and devices are not brought to patients. AstraZeneca supports federal research efforts designed to overcome key challenges in translational research, including the National Center for Advancing Translational Sciences (NCATS) at the NIH. NCATS also plays an important role in training translational researchers, for example, through its Clinical & Translational Science Awards (CTSA).

AstraZeneca was a foundational member of the NCATS Discovering New Therapeutic Uses for Existing Molecules Pilot Program and has provided multiple clinical compounds for third party research. The goal of the program is to use molecules that have already undergone significant research and development by the pharmaceutical industry to more quickly advance new treatments for patients. In 2013, NIH awarded $12.7 million to nine academic research groups for projects to explore new treatments for patients in eight disease areas, including two rare diseases. Three academic groups were successfully awarded grants for research on AstraZeneca compounds: Baylor College of Medicine for AZD0530 for Lymphangioleiomyomatosis, University of Virigina for ZD4054 for peripheral artery disease, and Yale University for AZD0530 for Alzheimer's disease. But for this program, it is unlikely that this research would be ongoing.

AstraZeneca recommends that the Committee vigorously support NCATS to achieve its goal of transforming the translational science process. A successful transformation of this process will facilitate the delivery of new treatments and cures for diseases to patients.

Development

Look to existing initiatives (such as the Clinical Trials Transformation Initiative and the TransCelerate initiative) for innovative ideas to modernize the clinical trial ecosystem. Multiple factors have contributed to the growth in size, complexity, and cost of clinical trials. Making clinical trials more efficient can help to reduce barriers to market for innovative medicines. Because transforming the clinical trial ecosystem is an enormous undertaking, the Committee should encourage all stakeholders, including government agencies, the biopharmaceutical industry, and academia, to work together to drive this transformation.

AstraZeneca holds leadership positions at two organizations dedicated to these efforts. First, the Clinical Trials Transformation Initiative (CTTI) is a public-private partnership intended to identify and promote practices that will increase the quality and efficiency of clinical trials. Second, TransCelerate BioPharma Inc. was launched in September 2012 to advance innovation in R&D, identify and solve common R&D challenges, and further improve patient safety. TransCelerate has established good working relationships with FDA, CTTI, and the Society of Clinical Research Sites, among others, to develop solutions to common challenges. For example, TransCelerate worked with FDA and other stakeholders to develop a position paper on risk-based monitoring methodology. FDA agreed to review sponsors' plans that incorporate this new methodology. TransCelerate has also worked with Clinical Data Interchange Standards Consortium (CDISC), Critical Path Institute (C-Path), FDA, NIH, and NCI to release new therapeutic area data collection standards for Alzheimer's Disease and asthma to streamline the process of developing new therapies for patients.

AstraZeneca recommends that the Committee explore the work of CTTI and TransCelerate to identify mechanisms to transform the clinical trial ecosystem.

Appropriately incentivize a healthy clinical research site landscape. Stable, sustainable clinical research sites are a fundamental element of a healthy clinical trial ecosystem. Without such sites, essential studies are delayed or abandoned altogether and the quality of the data produced may be compromised. These issues contribute to the challenge of bringing much-needed new therapies to patients. Investigators and clinical research sites unfortunately face growing financial difficulties, challenges with patient recruitment, and other operational hurdles that contribute to a high rate of investigator turnover across the clinical research landscape. AstraZeneca recommends that the Committee explore incentives and other mechanisms that can effectively contribute to site sustainability.

Encourage the development and regulatory acceptance of modern clinical trial designs, tools, and methodologies. FDA has traditionally required three phases of large scale, controlled trials as the basis for its review decisions. This traditional model is necessary in many cases, but in other cases, different approaches to clinical trials may be appropriate.

For example, in the antibiotics space, a core regulatory challenge is that the traditional FDA framework for approving antibacterial agents rests on the assumption that relatively large studies can be conducted for the pathogen(s) of interest at the body site(s) of interest. Although this approach may have worked well in the past, it is problematic for narrow-spectrum agents or those focused on specific types of emerging resistance. In these scenarios, the population of patients in whom these infections occur is limited and thus enrolling large numbers of patients into trials may be impossible or impractical. AstraZeneca encourages the Committee to consider the pending Antibiotic Development to

Advance Patient Treatment (ADAPT) Act (H.R. 3742), which proposes an innovative approach to antibacterial and antifungal drug development for serious or life-threatening infections where there exists an unmet medical need. This approach should allow the design of programs that might otherwise not have been attempted, for example, greater use of alternative trial endpoint designs. In addition, this approach will permit the agency to rely on different types of data to support approval, including preclinical and clinical data as well as datasets of limited size. This approach will encourage the development of greatly needed drugs for present problems and in anticipation of future medical crises.

In certain circumstances, FDA has used its existing regulatory flexibility to permit flexible clinical trial designs. For example, AstraZeneca and its biologics research and development arm, MedImmune, recently announced their involvement, along with several other public and private entities, in the Lung Cancer Master Protocol trial, or Lung-MAP, a multi-drug, multi-arm, biomarker-driven clinical trial for patients with advanced squamous cell lung cancer. AstraZeneca and MedImmune have two compounds in the Lung-MAP trial. The primary goal of the study is to match patients with promising new cancer treatments based on their unique tumor profiles. This is the first "basket" study – a study that starts with one or more targets allowing patients with multiple diseases to enroll in cohorts or groups – that could be used to support regulatory approval. This approach to clinical testing should not only improve access to promising drugs but also ease the significant recruitment and infrastructure burdens on researchers involved in traditional clinical trials.

AstraZeneca has encountered challenges, however, in gaining FDA acceptance of novel clinical trial designs outside the context of oncology therapies. AstraZeneca recommends that the Committee encourage FDA, particularly across review divisions, to embrace new ways of performing and evaluating clinical trials, for example, adaptive trials, seamless phase 2/3 studies, etc.

In addition to accepting novel clinical trial designs, the Committee should encourage or specifically authorize FDA to accept alternative approaches to gathering evidence for regulatory decision-making in both the safety as well as clinical efficacy contexts. For example, observational studies or alternative clinical designs may be an appropriate alternative to large cardiac outcome trials for non-cardiac drugs to address potential safety issues, but regulatory acceptance of these alternative approaches has varied. In the context of clinical trials, FDA should be encouraged or authorized to accept data from non-traditional sources, including, for example, real world evidence and data from electronic medical record (EMR) databases, claims databases, registries, and other appropriate, reliable sources.

New methods and techniques are also being developed for use in the preclinical and early clinical stages of drug development, and regulatory acceptance of these new tools is important. For example, AstraZeneca has collaborated with the Wyss Institute for Biologically Inspired Engineering at Harvard University to apply the Institute's advances in the development and validation of human organs-on-chips to develop new animal versions. Human Organs-on-Chips are composed of a clear, flexible polymer about the size of a computer memory stick and contain hollow microfluid channels lined by living human cells, allowing researchers to recreate the physiological and mechanical functions of the organ and to observe what happens in real time. As part of the collaboration between AstraZeneca and the Wyss Institute, researchers will compare human and animal organs-on-chips to understand the extent to which drug safety results in animals can predict how

an investigational drug might impact humans. This comparison is an exciting example of "predictive science," in which researchers harness the power of technology to better understand how a medicine might ultimately impact patients and in some cases, speed the delivery of innovative new medicines. The potential of these innovative technologies to transform drug development can only be realized if FDA accepts these new tools as part of the drug development process. Integral to this acceptance are highly qualified scientists who can interpret study data.

The use of validated drug development tools including biomarkers and patient reported outcome (PRO) measures has the potential to radically improve the drug development process. AstraZeneca serves in leadership roles on trade association committees looking to advance dialogue with FDA on nonclinical and clinical safety and efficacy biomarker complexity, context use, and evidence needed to support regulatory decision making. Despite this great potential, the FDA qualification/validation process for these tools has been slow and unclear. Improving communication between FDA Review Divisions and the Study Endpoints and Labelling Development (SEALD) Group, having consistent interpretation of 2009 PRO Guidance, and revisiting the role of consortiums such as the Critical Path PRO Consortium will help advance more patient-centric drug development approaches.

Meaningfully incentivize personalized medicine. Personalized medicine or personalized healthcare – that is, the tailoring of medical treatment to the individual characteristics, needs, and preferences of each patient – holds great promise to prevent disease, find the correct treatment more quickly, prevent side effects, improve patients' quality of life, and treat disease more effectively.

The concept of personalized healthcare is embedded in the AstraZeneca pipeline. Eighty-five percent of our pipeline follows a personalized healthcare approach, including the use of companion diagnostics and biomarkers to identify patients most likely to benefit from AstraZeneca medicines and to increase the successful use of drug products. Recently AstraZeneca scientists described a comprehensive longitudinal review of the company's small molecule drug projects from 2005 to 2010 and the establishment of the 5R's framework: the right target, the right patient, the right tissue, the right safety, and the right commercial potential to help improve R&D productivity. Many of these approaches are critical in the development of personalized medicines and can have impact on overall pharmaceutical R&D productivity. This work was recently published in *Nature Reviews Drug Discovery* and demonstrates AstraZeneca's commitment to targeting the right treatments at the right patients.

Despite the great promise of personalized medicine, much can be done to support the continued innovation and adoption of personalized medicine. Specifically, AstraZeneca recommends that the Committee explore mechanisms to create a transparent, stable, and predictable regulatory environment for personalized medicine products and technologies. Because multiple FDA Centers are involved in the regulatory review and decision making process for personalized medicines products (e.g., CDER, CBER, and CDRH), improved coordination and communication among the Centers may facilitate this process. In addition to changes in the regulatory environment, changes to reimbursement and payment policies may be necessary. Healthcare systems will need to address increasing biomarker complexity, new diagnostic technologies, growing amount and intersection of complex clinical and molecular information, and increased treatment algorithm complexity.

Encourage innovation across all therapeutic areas. A recent examination of the biopharmaceutical pipeline reveals that certain therapeutic areas, such as oncology, infectious diseases, and neurology, showed the greatest number of development projects.[1] A look at submissions to FDA by therapeutic area shows similar trends.[2] While innovation in these areas is certainly important and should be encouraged, new therapies in other therapeutic areas are also desperately needed.

AstraZeneca has observed that FDA acceptance of innovative approaches varies across review divisions. AstraZeneca encourages the Committee to evaluate what factors have contributed to more robust, successful, and innovative therapeutic areas. To the extent that this evaluation reveals that certain FDA review divisions follow managerial or scientific approaches that encourage innovation in a particular therapeutic area, the Committee should consider how these best practices can be applied consistently across all FDA review divisions.

Moreover, and as referenced above, the coordination and application of regulatory approaches across Centers is an ever-present feature of enabling the development of personalized medicines and their companion diagnostics. While the employment of diagnostic assays in clinical practice varies greatly across therapy areas, there is a need for consistency in how individual review Divisions interact with CDRH, how they interpret FDA policy and guidance with regard to investigational devices, and how they apply the regulatory framework where it links drugs and diagnostics. It is notable that the agency has made good progress here, and AstraZeneca encourages continued efforts in this area.

Delivery

Ensure payers, formulary committees, and similar entities have timely access to relevant information about medicines. FDA's approval of an innovative new product or approval of a new indication for an approved product is not the end of the path to bring new treatments to patients. Instead, in some ways, the approval decision is just the beginning. Today, payers, formulary committees, and similar entities heavily influence patient access to new therapies through coverage and reimbursement decisions. Innovative, important medicines do no good if patients cannot access them.

In the case of a new therapy or a new indication for an approved therapy, payers and similar audiences often need up-to-date scientific information prior to FDA product approval, to assist in scientific review related to coverage and reimbursement. This information allows decision makers to become familiar with a new product and address issues such as coding, coverage, or payment prior or proximate to the time of FDA approval, thereby avoiding delays in patient access to beneficial new uses and products. This process may become even more important as FDA approves more products under the accelerated approval pathway or as breakthrough therapies, where FDA may rely on different endpoints for approval than are used under the traditional approval pathway. Payers may require complete and accurate scientific data about these products in order to align standards for reimbursement and coverage with FDA standards for approval. And

[1] PhRMA, The Biopharmaceutical Pipeline: Evolving Science, Hope for Patients (January 2013), *available at* http://www.phrma.org/sites/default/files/pdf/phrmapipelinereportfinal11713.pdf.
[2] CHI, A Closer Look at FDA Drug Review Performance (June 2014), *available at* http://www.chi.org/wp-content/uploads/2014/06/CHI_FDA-report_FINAL1.pdf.

ideally, this alignment should occur prior to product approval so that patients may have timely access to the product.

Unfortunately, the rules governing manufacturers' ability to communicate this information to these entities lack clarity. Manufacturers look primarily to one statutory section and one regulation to guide their activities in this area. First, section 502(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) permits manufacturers to provide to "a formulary committee, or other similar entity" "health care economic information" that "directly relates" to an approved indication, so long as the information is based on "competent and reliable scientific evidence." Although this part of section 502(a) was enacted into law in 1997, FDA has yet to issue guidance or regulations clearly defining the contours of this section. Second, with respect to communication about a new treatment or a new indication pending approval by FDA, FDA's regulations prohibit manufacturers from engaging in preapproval promotion or commercialization of an investigational product but recognize that this prohibition is not intended to restrict "the full exchange of scientific information" concerning the investigational drug. *See* 21 C.F.R. 312.7(a). FDA has not adequately defined the terms "commercialization" or "exchange of scientific information" such that clear boundaries exist regarding permissible manufacturer speech to payers and similar audiences about an investigational product.

In the absence of such clarity, manufacturers must infer FDA's legal interpretation from FDA statements, court documents, and other publicly available information. A manufacturer's interpretation of the legal framework may not comport with the government's expectations, leaving the manufacturer vulnerable to enforcement action by FDA should the agency disagree with the manufacturer's interpretation. As a result, manufacturers may choose not to communicate legitimate and important speech about an investigational product to payers and similar entities. Patient access to the product upon approval may be delayed as these entities have not fully evaluated the product and made appropriate coverage and reimbursement decisions prior to product approval.

To address the lack of clarity surrounding the contours of permissible manufacturer communication with payers and similar entities, AstraZeneca recommends that the Committee direct FDA to establish clear and comprehensive guidance regarding this area. Any guidance or policy issued by FDA should be consistent with the principles and limitations of the FDCA as well as the First Amendment.

In addition, AstraZeneca recommends that the Committee include specific time frames by which FDA must issue this guidance. Although FDA, in response to two citizen petitions, recently promised to issue by the end of the year a number of guidance documents addressing manufacturer speech issues (including, distributing scientific and medical information on unapproved new uses and manufacturer discussions regarding scientific information more generally), no legislative mandate exists compelling the agency to fulfill that promise. Competing priorities and demands may occupy FDA's attention and limited resources. Specific, statutory time frames will require the agency to prioritize this desperately needed guidance. Clear and comprehensive policies regarding communication about medicines by companies to payers and similar entities are critical to ensure that patients receive timely access to important, new therapies.

Examine marketplace challenges and their impact on patient access to innovative medicines. Professional societies sometimes develop clinical practice guidelines or policy statements regarding specific disease states or medicines. In 2011, the Institute of

Medicine (IOM) released recommended standards for the best methods to use when developing clinical practice guidelines.[3] Professional societies should develop clinical practice guidelines in accordance with the IOM recommendations. The current process by which the societies develop these guidelines or statements is not always transparent to the public. Given this lack of transparency, it can be difficult to discern if the professionals serving on professional society advisory committees developing these guidelines have the appropriate expertise or if there is appropriate consideration of adequate, relevant information prior to the development of any practice guidelines.

The clinical practice guidelines or statements developed by professional societies that do not adhere to the IOM's rigorous standards may hinder patient access to treatments and therapies. For example, these guidelines or policy statements may contain recommendations for use that diverge from FDA's approved prescribing information. If the guidelines recommend a narrower patient population or dosing schedule than that provided for in the FDA-approved label, the outcome is typically that fewer patients will receive access to the product as payers and similar entities tend to follow the recommendations of professional societies for purposes of coverage and reimbursement. This outcome is particularly troubling for products intended for vulnerable pediatric populations. In addition, from the perspective of the manufacturer, this outcome presents yet another challenge to developing products for children and may further discourage innovation in this space.

Appropriately protect intellectual property

The process of innovation for new medicines is extremely complex, expensive, and lengthy, and a positive outcome – i.e., a FDA-approved new treatment for patients – is not guaranteed. Intellectual property protection ensures that biopharmaceutical research companies have the opportunity to recoup their costly and risky investments in these new medicines and provides incentives to support further innovation.

Industry dynamics and the financial, regulatory, and scientific environments overall have changed dramatically since Congress passed the Hatch- Waxman Act in 1984. Among other things, drug development has become more costly and challenging. In light of these changes, AstraZeneca believes that the current structure of intellectual property protection should be improved to sustain continued innovation. We encourage the Committee to explore alternatives to the current structure, including examining the regulatory exclusivity periods for small molecules. AstraZeneca encourages the Committee to take into account the evolving nature and business of science and to consider mechanisms that are flexible enough to not only incentivize today's research and development but also to incentivize research and development in the future.

In addition to strong intellectual property protection, AstraZeneca encourages the Committee to look at combinations of "push" and "pull" mechanisms to further innovation. "Push" mechanisms are ones that help decrease the cost of development, for example, tax credits, grants, and public-private partnerships. "Pull" mechanisms increase income linked to approval, for example, extended exclusivity, patent life, prizes, etc. Both types of tools may be necessary to fully incentivize the discovery, development, and delivery cycle for new patients.

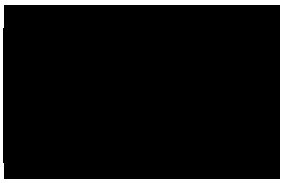
[3] IOM, Clinical Practice Guidelines We Can Trust (Mar. 23, 2011), *available at* http://www.iom.edu/Reports/2011/Clinical-Practice-Guidelines-We-Can-Trust.aspx.

Conclusion

AstraZeneca greatly appreciates the opportunity to provide these comments. We look forward to continued engagement with the Committee to explore ways to accelerate the discovery, development, and delivery of promising new treatments to patients. If you have any questions or would like any additional information on these or any other related topics, please contact either Jacqui Kirby or Theresa Jolivette in our Washington, D.C. office at 202-350-5500.

Sincerely,

Paul Hudson
President, AstraZeneca US and
Vice President, North America



Briggs W. Morrison, M.D.
Executive Vice President,
Global Medicines Development
and Chief Medical Officer