American Heart Association | American Stroke Association
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March 13, 2015

Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

Re: 21st Century Cures Discussion Document

Dear Chairman Upton and Representative DeGette:

On behalf of the American Heart Association (AHA), including the American Stroke Association (ASA) and over 22.5 million volunteers and supporters across the country, we appreciate the opportunity to provide comments regarding the 21st Century Cures Act discussion draft. We applaud your work and the significant attention the Committee on Energy and Commerce has given this initiative over the past year. In addition, we appreciate your continued commitment to engaging stakeholders to find ways to improve patient care and access to treatments. We are grateful for the numerous opportunities your Committee has provided the AHA/ASA and other stakeholders to inform this initiative, including allowing the AHA/ASA to provide testimony at the Subcommittee's laboratory developed test hearing on September 9, 2014.

We also commend the Committee for releasing its discussion draft and hope that you will continue to provide additional opportunities for stakeholders to share thoughts as the bill works its way through the legislative process.

While we share your overall goals of advancing biomedical research, engaging patients in the drug discovery and development process, and increasing access to critical drug therapies and products, it is crucial that any legislative proposal maintain necessary patient safety protections and ensures the efficacy of all medical products. Furthermore, it is important to recognize that the Food and Drug Administration (FDA) has made considerable progress in recent years in expeditiously bringing new, innovative products to market that improve quality of care for patients. In 2014, the FDA approved the highest number of novel new drugs since 1996, including 17 new therapies to treat rare diseases. The FDA's

existing regulatory authorities allowed it to evaluate and bring these new drugs to market while maintaining its rigorous safety standards. We strongly believe that these safety and efficacy safeguards must remain in place.

To that end, we have highlighted a number of provisions in the discussion draft that we believe, as currently written, do not strike the appropriate balance between reducing a patient's risk from harm while facilitating the discovery of better treatments and cures for cardiovascular diseases (CVD). These provisions primarily would change or accelerate processes within the FDA drug and device approval process, as well as allow new evidentiary standards to be submitted for review. We believe these provisions may have the potential to yield unsafe products for patients or expand access to products that may be prematurely determined to be safe and effective. We also must ensure that efforts to speed approval do not inadvertently undermine the recruitment of patients, particularly patients with diverse backgrounds, to later phase trials. In addition, we have also noted a number of proposed provisions that would make reforms at the National Institutes of Health (NIH) that we believe may have negative consequences on the agency and federally funded research initiatives.

There are, however, a number of provisions included below that we support and would encourage the Committee to include in future legislative drafts. In some cases, we have offered suggestions for ways they could be made even more beneficial for patients. We have also included suggestions for two provisions that are not currently in the bill. These include language in the bill that would expand the use of telestroke care – or the use of telemedicine in the treatment of stroke – by allowing Medicare to reimburse for telehealth services that originate in urban and suburban areas, as well as in rural areas, and a provision that would create new incentives for the development of high impact preventative medicines.

Overall, we applaud the Committee for exploring ways to expand opportunities for patients to provide input during the drug and biologic review process, create new public-private partnerships that would work together to bring new cures and treatments to patients, facilitate data sharing, and reduce economic burdens for patients to access the care they need. While we know there are many diseases without any treatment options or cures, we hope the Committee continues to recognize improving patient health outcomes in the United States depends not only on accelerating innovation in the drug and device discovery and development process but also requires that existing therapies for which there is well-established science and recommended use in authoritative guidelines are applied to the full effect for the benefit of individuals and population health. Therefore, we encourage the Committee to also consider the need for innovation in the dissemination and scaling up of existing interventions.

We recognize these are challenging issues, which is why we also remain committed to advancing promising approaches in the regulatory process that bring together all stakeholder perspectives to appropriately address the balance between comprehensive knowledge on the benefits and risks of therapies while providing timely patient access. For instance, the AHA/ASA considers the concept of adaptive licensing as one potential approach to aligning a patient's need for access to new treatments with the desire to spur innovation and to maintain rigorous safety oversight. In short, an adaptive licensing approach would provide regulatory flexibility by allowing provisional approval of a product when combined with ongoing evaluation, surveillance, and

evidence gathering prior to granting full approval. Such an approach, especially when coupled with ongoing communication between patients and practitioners that acknowledges the evolving uncertainties of products and their use as additional knowledge is gathered, may be an additional concept for the Committee to explore as it seeks to address current challenges in the drug and device approval process.

We hope that the Committee carefully considers the following comments as it works to advance this legislation.

Title I – Putting Patients First By Incorporating Their Perspectives into the Regulatory Process and Addressing Unmet Needs

Section 1001
We support the need to expand opportunities for patients to provide input during the drug and biologic review process. Patients can provide a unique perspective on the impact of a disease, the severity of the condition, and the adequacy of the existing treatment options. Patients can also provide valuable information on the benefits they would like a drug to deliver and the acceptable level of risk. There are currently a number of cardiovascular diseases, including atrial fibrillation, stroke, and peripheral arterial disease, that affect a signification portion of the U.S. population and affect functioning and activities of daily living yet lack drug therapies that sufficiently address treatment needs. We agree that there should be a framework for incorporating the patient experience into the regulatory decision-making process, and we would look forward to working with the FDA in creating and implementing the framework proposed in this legislation.

Sections 1021-1024
We appreciate the Committee's interest in developing and revising standards for determining qualified surrogate endpoints and finding new ways to approve therapies, as well as allowing the FDA to enter into partnerships to review requests for qualifying biomarkers for use other than as surrogate endpoints. We understand that this provision is reasonable for certain disorders and therapeutic strategies, and it could be potentially valuable when a surrogate marker appears to predict toxicity in a subset of a target population. We would like to strongly caution the Committee, however, that these provisions may also adversely affect the public health should a biomarker be falsely accepted as a surrogate endpoint without robust scientific evidence, particularly as there are many examples of flawed reliance on surrogates in the evolution of cardiovascular pharmacologic therapies. For instance, there have previously been biomarkers that represented plausible surrogate endpoints – such as reduced rate of ventricular premature beats following a heart attack or cardiac output in congestive heart failure – that failed to predict the expected clinical benefit when tested in outcome trials. As a result, using biomarkers as surrogate endpoints which are later discovered to not improve health outcomes could allow for the approval of products that cause harm or death in certain patient populations.

Sections 1041, 1081-1082, and 1101
We recognize the Committee's intent to find ways to accelerate processes for bringing new breakthrough drugs and devices to market. We also believe that the FDA shares this desire, as it currently has existing pathways to achieve this goal while providing broad discretion and

flexibility in applying statutory standards for safety and efficacy. This includes the use of existing pathways for exceptional patient access to early stage investigational drugs for treatment use (21 CFR part 312, subpart I) and for drugs intended to treat life-threatening and severely-debilitating illnesses (21 CFR part 312, subpart E). As currently written, we believe that the provisions that rely on very early stage clinical safety and efficacy data are overly broad, subject to misinterpretation, and have the potential for major risk of patient harm or costs from unanticipated complications. The reliance on early data from shorter, smaller trials could potentially result in the approval of drugs or devices based on insufficient evidence regarding efficacy and, importantly, safety. This could ultimately be particularly detrimental for women, minorities and the elderly, who are frequently underrepresented in early phase trials even more than they are in phase 3 trials.

On the other hand, we believe provisions that would accelerate the approval of breakthrough devices could be potentially beneficial for a limited subset of medical devices. However, provisions in the discussion draft should be tailored so that accelerated approval would be used sparingly. The goal should be to target true breakthrough products and only those that are rigorously qualified for major unmet clinical needs or represent major innovations.

Moreover, we caution that, although Section 1082 is currently placeholder language, the Committee should not include language that would require Medicare and Medicaid to cover a device approved through the priority review for breakthrough device process because the device may not be appropriate for the Medicare population.

Section 1181
We caution the Committee that efforts to create a streamlined data review program for new indications could undermine efforts to ensure a sufficiently robust dataset to allow appropriate demographic subgroup analyses for safety and efficacy, particularly if the test for the initial indication was conducted in a relatively homogeneous population. Such subgroup analyses by sex, race and ethnicity, and age can help to lead to better-targeted therapies, the ultimate goal of precision medicine initiatives.

Section 1241
While we recognize the need to create incentives for industry to invest in new products that would lead to fewer adverse events and increase patient benefits and adherence, we are concerned that this provision could make drugs more expensive for patients by extending exclusivity. While such a provision might be beneficial for a limited subset of products, such as those to treat certain rare diseases and certain preventative medications, we believe strongly that patients should have access to affordable medications and caution that such a provision could delay access to generic, lower-cost drugs. We emphasize this point since multiple studies have shown the disturbing fact that many patients do not comply with a prescribed, evidence-based regimen because of cost.

However, we strongly encourage the Committee to include a narrowly crafted provision that would create a process to extend patent life for high impact preventive therapies to allow greater innovation by industry, improve chances of successfully decreasing burden of illness, and improve public health. The long duration of follow-up required for primary prevention trials

often erodes the patent life of a drug, leaving little financial incentive for companies to invest resources in this area. This is particularly an issue for stroke research and neurodegenerative diseases. Clinical trials to test the efficacy of preventive strategies for stroke would require early interventions and prolonged follow-up, perhaps decades, to show effects. The long duration of these clinical trials represent a substantial portion of a drug patent, making it prohibitive for companies to even consider developing drugs for prevention.

Title II – Building the Foundation for 21st Century Medicine, Including Helping Young Scientists

Section 2001
We applaud the Committee for including this provision. We strongly support collaboration across all stakeholders and sectors of the health care system to advance new cures and treatments for patients.

Sections 2061-2063
We believe this is an important issue for the Committee to consider, due to the great potential for innovation for mobile technologies that could improve patient health. We also understand, however, that the FDA is currently addressing similar issues and how it would oversee these types of technologies. It is important when both the Committee and the FDA consider additional oversight or regulation of medical technologies they consider how this might increase regulatory hurdles, particularly for clinical decision support software, and how this would impact patient management.

Sections 2081-2092
Expanding access and enhancing clinical trials transparency, as well as allowing qualified clinical data registries to access Medicare data, could have major potential for quality improvement and research purposes. For example, the AHA/ASA has developed a number of quality improvement programs that include clinical registries to aggregate patient care data and generate real-time reports for providers that assess their performance compared to national benchmarks. Access to timely Medicare data would enhance these quality improvement efforts, and we encourage the Committee to provide clarity as to the timeliness of the Medicare claims data that would be available, as well as clarify that if a registry is a "qualified clinical data registry" for the purposes of the Centers for Medicare and Medicaid Services (CMS) quality reporting programs then access to Medicare claims data should be provided at no cost to such entities or organizations. It is imperative that claims data be timely in their release. As noted above, registries can provide real-time information and if the lag for administrative data is too far behind the clinical data, access to that data would not provide any significant benefit. We also recommend that the Committee provide additional clarity about the need to develop and implement appropriate use criteria as part of the data-sharing framework and wish to emphasize that we look forward to working with the Committee on establishing the principles for responsible data-sharing.

Section 2101
We recognize that the intent is to expand access to data that may be useful in the FDA approval process beyond the current data standards, such as pragmatic "real world" randomized controlled trials embedded within registries and electronic health records to generate a high level evidence at lower cost. While the FDA should be encouraged to consider this type of data, this provision should not confound useful data with the "real world" observational data emphasized in this provision. Additionally, the Committee should clarify that the "real world evidence" described in this section, as currently written, should only be used for postmarket approval processes and not for primary approval of new therapies.

Section 2121
We support this provision and believe it is important for Medicare to cover the cost of medical devices that are for coverage with evidence development that a beneficiary receives in order to ease the economic burdens of accessing these treatments.

Section 2161
We have previously submitted more detailed comments on the regulation of diagnostic devices and laboratory developed tests (LDTs), as well as provided testimony on this issue during a September 9, 2014 Subcommittee hearing. To briefly reiterate our previous comments, we support the FDA's recently released draft guidance documents and its proposed approach for regulating LDTs in a phased-in, risk-based manner. We believe this is the best approach for ensuring the appropriate level of oversight for LDTs in order to reassure patients and providers on the reliability and usefulness of these tests. We strongly encourage the Committee not to include language in any legislative proposal that impedes or prevents the FDA from acting swiftly to finalize its guidance and phasing-in regulation of these tests.

Section 2181
While this section is only a placeholder, we look forward to reviewing this provision and believe that it is important that health IT systems can adequately communicate with one another in order to improve patient care, particularly as patients with CVD and stroke frequently require multiple providers to manager their conditions.

Section 2201
We support this provision in principle and believe there are already policies in place to encourage data sharing, such as the NIH requiring certain applicants to address data sharing in their funding applications. We encourage the Committee to include additional clarity and information on this provision and how it would be implemented in order to ensure the appropriate governance of shared data – such as the timeframe when data would need to be made public – in order to allow the primary researchers the appropriate opportunity to publish their research.

Section 2221
We believe that expanding access to patient health information while providing sufficient protections could be a potentially powerful tool to address critical research needs. However, we ask that the Committee provide additional clarity as to what type of health care data these provisions would apply to, whether or not it includes health data collected as part of routine care,

how this would apply to specific episodes of care in addition to care taking place over a course of time in multiple health care settings, and how to make captured data meaningful to improve patient care.

Section 2241
We support this provision and recommend the Committee acknowledge and recommend using clinical registries as a mechanism for such a longitudinal study.

Section 2301
We support the Committee's interest in fostering precision medicine and look forward to reviewing language under this section in future legislative proposals. We strongly believe that precision medicine research will help arm us with a deeper understanding of the deadly diseases that affect so many Americans, including CVD. Like the Committee, the AHA/ASA is also committed to cutting-edge heart and stroke research in pursuit of personalized cures. That is one of the major reasons why we launched the Cardiovascular Genome Phenome Study (CVGPS) last year. CVGPS combines the power of long-term population studies with genomic analysis for a 360-degree look at heart health and disease. Precision medicine initiatives are essential for tapping research for hidden insights that will speed the discovery of better treatments to improve the cardiovascular health of our nation.

Title III – Modernizing Clinical Trials

Section 3002
We support this provision and the concept of a central institutional review board to help minimize regulatory duplication and unnecessary delays in research.

Section 3031
We are concerned that allowing the FDA and sponsors to periodically evaluate whether post-approval studies remain scientifically warranted could potentially lead to fewer postmarket studies and give too much flexibility for manufacturers to renegotiate their postmarket study requirements.

Section 3041 and 3061
We support these provisions and encourage the Committee to increase resources to support pediatric research.

Title IV – Accelerating the Discovery, Development, and Delivery Cycle and Continuing 21st Century Innovation at NIH, FDA, CDC, and CMS

Sections 4001, 4003, 4004, and 4005
While we support these provisions in principle and appreciate the Committee's interest in addressing accountability at the NIH and requiring planning to accelerate the discovery of new cures, we strongly caution the Committee not to duplicate efforts already underway at the NIH or place additional burdens on the NIH that would divert its ongoing research initiatives. For example, the FY2015 omnibus appropriations legislation included a similar provision to require the NIH to issue a strategic plan. As currently written, it is not clear how the strategic focus

areas will be determined, even though the language would ensure that certain diseases are given priority, and how these strategic areas will affect resource allocation decisions. We also cannot support provisions that require term limits of NIH institutes and center directors, and provisions that would require institute or national center directors to personally review and approve grants. We support language that may be included in Section 4003 that would better facilitate and ease travel restrictions for NIH researchers.

Sections 4002, 4007, and 4008
We support these provisions and the need to reduce administrative burdens on research. We also strongly support and encourage the Committee to include additional funding for NIH.

Section 4021
We support this provision and recommend that the language specifically include references to stroke. We understand that the text is currently drafted to ensure that a surveillance system be developed for all neurological diseases, and it would not be possible to mention all such diseases. However, we believe that it would be appropriate and helpful to mention stroke, particularly as it is the 5th leading cause of death, the leading cause of long-term disability, and the 2nd leading cause of dementia in the United States. We also recommend specifically mentioning rehabilitation as part of the information collected and stored in the surveillance system under subsection (c)(3)(D). In addition to information related to the incidence and prevalence of neurological diseases, we also recommend that the surveillance system collect data on recurrence rates for neurological diseases, as well as extend the scope to include major cardiovascular events and heart failure while providing sufficient funding to support this added scope of surveillance.

Section 4161
We support this concept and agree that reform is needed for the Medicare local coverage determination process, particularly as there is the need for consistency of local and national coverage determination processes and encourage the Committee to align the public comment period for national coverage determinations with this provision.

Section 4181
We have previously submitted more detailed comments about the Telehealth Subtitle to the Committee's telehealth working group and look forward to seeing a revised version of this section soon that will hopefully address these comments. To briefly reiterate our earlier comments, however, while we support the intent of this provision, we are concerned that it leaves too much discretion to CMS to develop a list of telehealth services covered under Medicare Part A and B when CMS has not yet acted within its current authority to support telehealth services. In addition, we believe that this provision would place certain requirements on CMS to certify services – such as ensuring that covered telehealth services would reduce Medicare spending, as opposed to federal health spending, or be budget neutral – that would make it difficult to expand these services.

We also strongly encourage the Committee to address the Medicare reimbursement barrier that would help make telestroke care more widely available by allowing Medicare to reimburse for telehealth services that originate in urban and suburban areas, as well as in rural areas.

Numerous studies have demonstrated that the use telestroke can be helpful in improving access to high quality stroke care. The use of telestroke has shown great promise in improving patient access to recommended stroke treatments in both rural and other "neurologically underserved" areas – enhancing access to high quality stroke consults and increasing the number of patients who receive tPA by six-fold in some hospitals. Moreover, the outcomes for stroke patients who are cared for in hospitals with telemedicine support have been comparable to those achieved in other stroke centers and have surpassed those achieved by general hospitals without telemedicine support or stroke units.

In addition to improving access to the recommended care, we believe the greater use of telestroke will also result in healthcare cost savings to the federal government by reducing disability and the need for more extensive medical care. Several studies have clearly shown that the use of tPA is cost-saving for stroke care, including a study published in the *New England Journal of Medicine* that showed patients receiving clot-busting therapy were at least 30 percent more likely to have minimal or no disability at three months when compared to patients who did not receive this treatment. The study also found that these patients have shorter hospital stays and are more frequently discharged to their homes rather than to more costly nursing homes. Another study found that the average cost savings when administering tPA was $4,255.00 per treated patient, largely as a result of decreased need for nursing home care and decreased utilization of rehabilitation by the patient who received treatment. We have provided the Committee's telehealth working group with legislative language for this provision and strongly urge that this be included in future drafts of the bill.

Section 4362
We support this provision and efforts to improve care for children with complex medical conditions, such as congenital heart defects.

Section 4381
We support this provision and the need to exclude continuing medical education from requirements under the Sunshine Act. We urge the Committee to include an additional exemption for indirect payments to voluntary health agencies (VHA) when the manufacturer gives complete discretion to the VHA to select the recipients of research funding.

Title V – Modernizing Medical Product Regulation

Section 5062
As noted above, we have significant reservations about using certain "real world evidence" as the basis for determining effectiveness of drugs and devices. This provision is also particularly concerning as it would constrain the FDA from requiring the submission of data from studies published in peer-reviewed journals. One potential consequence could mean that the FDA may not be able to determine whether or not there was adequate representation of patient subgroups in such studies in order to ensure that products are safe and effective for all who might use them.

Conclusion

We thank the Committee for providing the opportunity for the American Heart Association/American Stroke Association to provide feedback on the 21st Century Cures Act discussion draft. We applaud the Committee and staff for the significant amount of energy and attention it has given this initiative and agree with the Committee's intent to find new ways to discover, develop, and deliver new cures for patients. As you address these challenges, we strongly encourage the Committee to maintain processes that are necessary to maintain the rigorous review of the safety and efficacy of medical products before they are approved for use. It is critical that any legislation keep the appropriate balance between accelerating the drug and device discovery process and ensuring products are safe and effective for patients. We also encourage the Committee to recognize and explore ways to also facilitate innovation in disseminating information and the scaling up of existing interventions. Finally, it is critical that the Committee ensure the FDA, NIH, and other agencies have the resources they need should new requirements be placed on them.

While we noted several provisions that we support and are encouraged to see included in the draft legislation, we also believe there are a number of provisions identified above that do not appropriately balance patient safety needs with the desire to bring new drugs and devices quickly to market. We hope that these concerns will be addressed during the legislative process. If you have any questions or would like to discuss any of our comments and recommendations, please contact Kevin Kaiser at 202-785-7931 or via email at kevin.kaiser@heart.org.

Again, thank you for your careful consideration of our comments, and we look forward to continuing to work with the Committee on these critical issues.

Sincerely,

Elliott M. Antman, MD, FAHA
President
American Heart Association