Society for Women's Health Research

February 12, 2015

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

The Honorable Diane DeGette
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, D.C. 20515

Dear Chairman Upton and Representative DeGette:

On behalf of the Society for Women's Health Research (SWHR), we would like to thank you for providing the opportunity to comment on the current 21st Century Cures Discussion Draft.

We support the work of the "21st Century Cures Initiative" and its efforts to accelerate the discovery, development, and delivery of new medical treatments and cures to patients. We also appreciate the approach to this task, which has provided a systematic examination of the needs of the country's biomedical infrastructure and the essential tools and investments that our federal agencies will need to maintain the United States' standing as the leader in biomedical research and innovation. SWHR has long advocated for sustained investment in biomedical research and has specific recommendations enumerated on the discussion draft that are discussed in greater detail in the document below.

SWHR is a national nonprofit organization based in Washington, D.C. dedicated to improving women's health through advocacy, education, and research, and is widely recognized as the thought leader in promoting women's health research and sex-based biology. Since its founding 25 years ago, SWHR has been a strong advocate of greater public and private funding for basic science and biomedical research that can advance scientific knowledge, transform the quality of medical care, and enable personalized evidence-based treatment options for women. Our organization was instrumental in securing the mandate to include women and minorities in federally funded research in the passage of the National Institutes of Health (NIH) Reauthorization of 1993.

Science has demonstrated that the future of medicine lies in

developing therapies to targeted populations, yet women and minorities are still vastly underrepresented in the medical research enterprise. Much work remains to be done to combat this inequity. Part of that effort is the continuing need to increase knowledge of the importance of sex and gender differences during all phases of medical research so that clinical trials can be designed to truly reflect patient populations and lead to improved treatments.

Issues surrounding the collection, analysis, and usage of data are fundamental components of the discussion draft, as all research relies upon the strength of data generated. Medical research could be revolutionized by appropriately capturing, analyzing and translating better demographic data to researchers, physicians, and patients. SWHR has long argued that all stages of biomedical research must include sex as a fundamental biological variable where appropriate. In 2001, the Institute of Medicine (IOM) definitively confirmed that being male or female, was an important "basic variable that should be considered in designing and analyzing studies in all areas and at all levels of biomedical and health related research.[i]" Unfortunately, sex is still not considered a critical variable in most basic biological studies and research data is generally not analyzed by sex or by other critical subgroups (i.e. age, race, ethnicity) when it is published. This lack of attention to and recognition of the importance of data as fundamental as one's biological "sex" must be addressed in our biomedical and health research infrastructure, both public and private, in order to improve research and the translation of that research to the patient.

Outlined below by Title and Subsection SWHR has identified specific areas of interest and or concern. We hope the Committee will find our comments helpful as you continue to work on this important effort.

Title 1- Putting Patients First By Incorporating Their Perspectives Into the Regulatory Process and Addressing Unmet Needs

Subtitle A – Patient Focused Drug Development

Section 1001- SWHR believes that additional methodological considerations need to be incorporated in Title 1- Subtitle A Section 1001-(a) (y) (2) under the meaning of "patient experience data." These additions would be "patient desired outcomes from new therapies or treatments" and "patient perspective in the decision over assessing benefit versus risk". These additions also need to be incorporated into section 1001-(b) (1)(B) (i), pertaining to the data points to be collected under the guidance document.

Subsection D- Antibacterial and Antifungal

Section 1064- The language in the discussion draft presumes that antifungal and antibacterial research trials are appropriately populated with a diverse cross-section of the population impacted. SWHR believes this presumption is not accurate and that there is not sufficient representation from women and minorities in such medical research used to develop these therapies. This belief is backed by information released on November 21, 2014 on the Food and Drug Administration's Drug SNAPSHOT website which indicated that one antifungal drug, Jublia, was approved in June 2014 with only 23% women in the trial[ii]. Additionally, minority representation was very low, with African American participation at 5.9%[iii].

Subtitle E- Priority Review of Breakthrough Devices and Accelerated Approval

Section 1081-– SWHR is concerned with language included in Section 515B(b)(2)(c) that would allow for a sponsor to conduct post market data collection to verify clinical benefit or effectiveness after the device has been approved. Priority review and approval of devices should not be allowed when there is inadequate clinical trial data due to insufficient representation of women and minorities to

determine safety and effectiveness in these populations. Many device trials, particularly those in the area of cardiovascular disease (CVD) frequently lack adequate representation of women, minorities and the elderly to thus determine statistical significance or clinical relevance. This lack of adequate representation in CVD trials would only be exacerbated by allowing priority review and accelerated approval. The FDA approval process needs to ensure that a medical product is safe and effective in the populations it is intended to be used in. There is simply too much we do not know about the impact of hormones, reproductive status, body structures, and other differences between women, men, and the impact of age, race, and ethnicity for these to be discovered post approval and after adverse events and side effects are captured. This does a disservice to a large section of the population and is a safety issue. Post-market surveillance, while a valuable source of information that needs adequate FDA monitoring and enforcement, is not enough and should not be the norm or a substitute for what should be discovered in premarket approval.

Companies will meet FDA mandates regarding clinical trial representation (recruitment and retention) to avoid any delay in review and consideration of their applications. If applications must include appropriate subpopulation representation and analysis, then sponsors will ensure that clinical trial participation will change at all phases, and less will need to be discovered post market, often years after approval and use. **We strongly recommend that this draft not provide for this acceleration to market without appropriate study of safety and effectiveness on the populations for which device is intended.** SWHR firmly believes that FDA will work with sponsors and patient groups to address the many gaps in knowledge that do exist as well as representation/participation to capture all potential information possible in a trial prior to approval.

Subtitle J- Streamlined Data Review
Section 1181-SWHR supports a streamlined review process for adding indications to a drug label; however, we feel that the current language makes a presumption that current data demonstrating safety and effectiveness actually includes all demographic subgroup populations, in particular women and minorities, which is often not the case (see previous comment). Language in Section 505F (b)(5) should state that the full data sets submitted to the Secretary and summary data include demographic subgroup analysis.

Title II – Building the Foundation For 21st Century Medicine, Including Helping Young Scientists
Subtitle F- Building a 21st Century Data Sharing Framework
Section 2081- In clinical research, SWHR still believes that there is insufficient standardization in our clinical trial data collection process which causes researchers to lose a great deal of demographic data that could shed significant light on medical product usage, safety, and effectiveness among women and minorities.

Subtitle G – Utilizing Real World Evidence
Section 2101- SWHR remains concerned that not all available post market data generated by biopharmaceutical companies on real world medication use is reaching health care providers and patients due to restrictions from the FDA, particularly concerning pregnant women, for whom all medicines are generally prescribed off label. We believe open and transparent communication of important scientifically accurate data is important to advancing medical treatments in the digital age and key to fostering discovery and quicker translation to patients.

Companies collect data directly through clinical research, observational studies, exposure registries and medical record research in order to help inform them on the medical decision process and to

drive new research and innovation. They examine comparative data on the actual real world use of approved medicines and look at comparisons between two or more therapies. Further, companies look at sub-populations for safety and effectiveness, including sex and race, to advance scientific knowledge and the opportunity to potentially help healthcare professionals tailor their treatment to meet the needs of individual patients.

Companies are generally restricted by FDA from proactively sharing much of the data that they collect that exists outside of the package insert (PI) and may not add it to the labeling information for usage, as this would be considered a new indication and such data may not have been generated as part of the clinical trials for drug approval. SWHR believes language should be inserted in the proposed guidance in Section 505H(c) that allows for appropriate communication on real world medication use between health care providers and patients, quality of care received, and informed medical decisions on the off label usage of drugs, particularly in pregnant women, if the provisions outlined in Section 505H(c)(2)(a)(b) are met. Access to company data should be established in a way that provides for appropriate communication to health care professionals and patients on medication usage that could improve patients' health outcomes. In particular, subgroup analysis can shed light on important sex differences that will help physicians tailor treatments differently to their male and female populations. For example, companies are required to collect this data in exposure registries by the FDA when a medication is used by pregnant women (as all medications used during pregnancy are off-label) but they are not allowed to discuss any of their findings from their registries directly with health care providers or patients.

SWHR would suggest that this real world data be made accessible and transparently shared with open equal access to all stakeholders from researchers, clinicians, patients and the government as it is critical to ensuring that patients are receiving the most effective care possible.

Additionally, SWHR recommends that the proposed guidance include in Section 505H(c)(2)(B) recommendations on when such data from real world use would trigger FDA requirements for a submission of a new indication for the medical product, and what that process should be to seek such additional indication in light of the real world data, particularly for populations, such as pregnant women where research is restricted or where sufficient numbers of patients for additional research trials are harder to obtain.

Title III – Modernizing Clinical Trials

Subtitle A – Clinical Research Modernization Act

Section 3001- SWHR recommends that the following language be added after Section 491A(b)(3)(B) to instruct IRB's, central, multisite, single and local, to take into account inclusion of both sexes in dual-sex clinical trials and that other demographic subgroups (such as race, age and ethnicity) are adequately represented, data standardized and appropriately analyzed to ensure clinical trials are designed to maximize efficiency.

Subtitle B – Broader Application of Bayesian Statistics and Adaptive Trial Design

Section 3021- SWHR believes our medical research enterprise, including NIH and FDA, should be provided appropriate authority and flexibility to implement a more strategic and efficient trial design to meet the needs of a 21st century research design.

We believe that the discussion draft should include language in Section 507B(b) that requires the FDA and NIH to eliminate unnecessary exclusions (such as the automatic exclusion of anyone over

age 75 or pregnant women) from clinical trial protocols, to the maximum extent feasible. As a general rule, FDA and NIH should seek to ensure that study participants reflect the real-world population for which the treatment/intervention will ultimately be used.

Additionally, language should be inserted after Section 507B(b)(2)(3)that requires FDA to establish an ongoing Advisory Committee for **subgroups underrepresented in clinical research studies** (women, minorities, the elderly) that will make recommendations to improve participation rates, analysis of subgroup data, reporting and making publically available all subgroup data. This Advisory Group would be similar to the FDA's Pediatric Advisory Committee. The voting members should include at least one representative from a relevant patient or patient-family organization and one representative that represents consumer interests and is recommended by either a consortium of consumer-oriented organizations or other interested persons.

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

Subsection A – National Institutes of Health

In 2014, the National Institutes of Health (NIH) signaled that they will be developing policies that require applicants to report their plans to balance male and female cells and animals in preclinical studies in all future applications, unless sex-specific inclusion is unwarranted, based on rigorously define exceptions. We believe that the 21st Century Cures Discussion Draft could provide the NIH with appropriate incentives and accountability to codify the development and full implementation of these policies. NIH is considered the world leader in biomedical research. When NIH implements policies that stress the importance of biological sex as a fundamental variable in research and require analysis of data by sex as a part of grant progress reporting and published results, others will follow suit.

SWHR proposes that the Committee include the following language under Title IV, Subsection A, Section 4001- of the current 21st Century Cures discussion draft.

1. Authorize NIH to develop policies that require research applicants to report their plans for the inclusion of male and female cells and animals in preclinical studies in all future applications, unless sex-specific inclusion is unwarranted, based on rigorously defined exceptions. No later than one year after enactment of this legislation NIH shall publish the draft policy via a notice of proposed rulemaking to allow for public comment and response. The expansion of such current policies shall include plans for:

    a. Investigators to prominently indicate the sex of their experimental model in their grant application and progress reports.

    b. Investigators studying one sex should provide justification as to why the study is limited to one sex as a part of the grant reporting process and in published reports. When studying both sexes, investigators should report, and when appropriate, analyze their data by sex as part of grant progress reporting to the Agency and in published results.

    c. Investigators to consider sex as a biological variable in relevant research on animals, cells, and human subjects.

2. Direct NIH to monitor compliance of sex and gender inclusion in preclinical research funded by the agency through data-mining techniques that are currently being developed and implemented. Encourage NIH to work with publishers to promote the publication of such research results.

3. Authorize the Director of the NIH to establish a Trans-NIH Working Group on Sex Differences in Research, which shall be comprised of representatives of each Institute and Center, the Office of Research on Women's Health, as well as appropriate members of the scientific and academic communities and patient organizations as determined by the NIH Director. Additionally, the Working Group shall ensure appropriate implementation of the regulations proposed above; determine the progress of NIH's strategic plan on sex difference in research and to ensure open collaboration between ICs on this matter. The Working Group shall provide a written report to the Director to be included in the NIH biannual report that details the inclusion of females and advances in sex differences in pre-clinical research and include the proportion of women and minorities as subjects in clinical research participant enrollment by trial phase and in all studies of human subjects, the proportion of studies that incorporate sex as a biological variable and of those studies which analyze data by sex as part of grant review, award, and oversight processes and this data should be reported by Institute and Center across the Agency.

4. The National Library of Medicine is urged to implement changes to Clinicaltrials.gov that will require users to input the number of participants that drop out of trials and break those participants out by sex/gender and race. Such data should be provided for all phases of clinical trials to the extent possible.

5. Authorize the Specialized Centers of Research on Sex Differences program, to support interdisciplinary collaborations on sex and gender influences in health, and bridges basic- and clinical-research approaches. This program also facilitates training in sex and gender considerations in experimental design and analysis.

Section 4004- Increasing Accountability at the National Institutes of Health
SWHR agrees with efforts to increase accountability at the NIH; however, we do not agree with usage of percentages to determine investments in both intramural and extramural research. Basic science investments should flow into areas that are most promising, which due to the nature of science, cannot be pre-determined or predicted. We believe that the NIH Director with the critical input of Institutes, Centers and Offices Directors should have the flexibility to best determine investments in research proposed.

Subtitle S – Continuing Medical Education Sunshine Exemption
Section 4381- CMS's efforts to clarify reporting under the Physician Sunshine Payment Act has resulted in confusion and inconsistency. SWHR believes that there should be language added after Sec.4381 (b) which addresses what is a reportable indirect payment in order that manufactures truly understand when reporting is required and when it is not.

The lack of clarity in reporting and exemptions is causing great confusion and frustration for nonprofit organization and other stakeholders as it directly impacts participation of scientists, researchers and clinicians in important scientific forums and meetings. SWHR understands that only applicable manufacturers and applicable group purchasing organizations (GPOs) have reportable

payments or other transfers of value, ownership or investment interest, or both are required to register and report in Open Payments (FAQ 9138). In general, all direct or indirect payments or transfers of value made by an applicable manufacturer to a covered recipient (physician or teaching hospital) must be reported in Open Payments. As described in 42 C.F.R. §403.902, an indirect payment is a payment or other transfer of value made by an applicable manufacturer to a covered recipient through a third party, where the applicable manufacturer requires, instructs, directs, or otherwise causes the third party to provide the payment or other transfer of value, in whole or in part, to a covered recipient. An exclusion applies if the applicable manufacturer does not know the identity of the covered recipient during the reporting year or by the end of the second quarter of the following reporting year.

If an applicable manufacturer provides an unrestricted payment or transfer of value to a third party to use at the third party's discretion, this would not constitute an indirect payment (78 FR 9490). This unrestricted payment should not have to be reported but unfortunately there is insufficient assurance to the manufacturers to date causing them to require reporting unnecessarily directly impacting scientific discussion.

SWHR appreciates the hard work the committee has done to reach a comprehensive discussion draft of this magnitude and for being allowed to provide extensive to the review process. We hope that you will find our comments helpful as you review and refine the draft legislation. We look forward to working with the Committee going forward to you endeavor to transform the US biomedical enterprise.

Sincerely,

Martha Nolan
Vice President, Public Policy

Leslie Ritter
Director, Government Affairs

[i] Wizemann TM, and Pardue, Mary-Lou, eds. Exploring the Biological Contributions to Human Health: Does Sex Matter? Washington, D.C.: National Academies Press; 2001.2-11
[ii] FDA Website. Drug Trials Snapshot: Jublia (efinaconazole). http://www.fda.gov/Drugs/InformationOnDrugs/ucm422419.htm. Accessed February 9 2015.
[iii] FDA Website. Drug Trials Snapshot: Jublia (efinaconazole). http://www.fda.gov/Drugs/InformationOnDrugs/ucm422419.htm. Accessed February 9 2015.