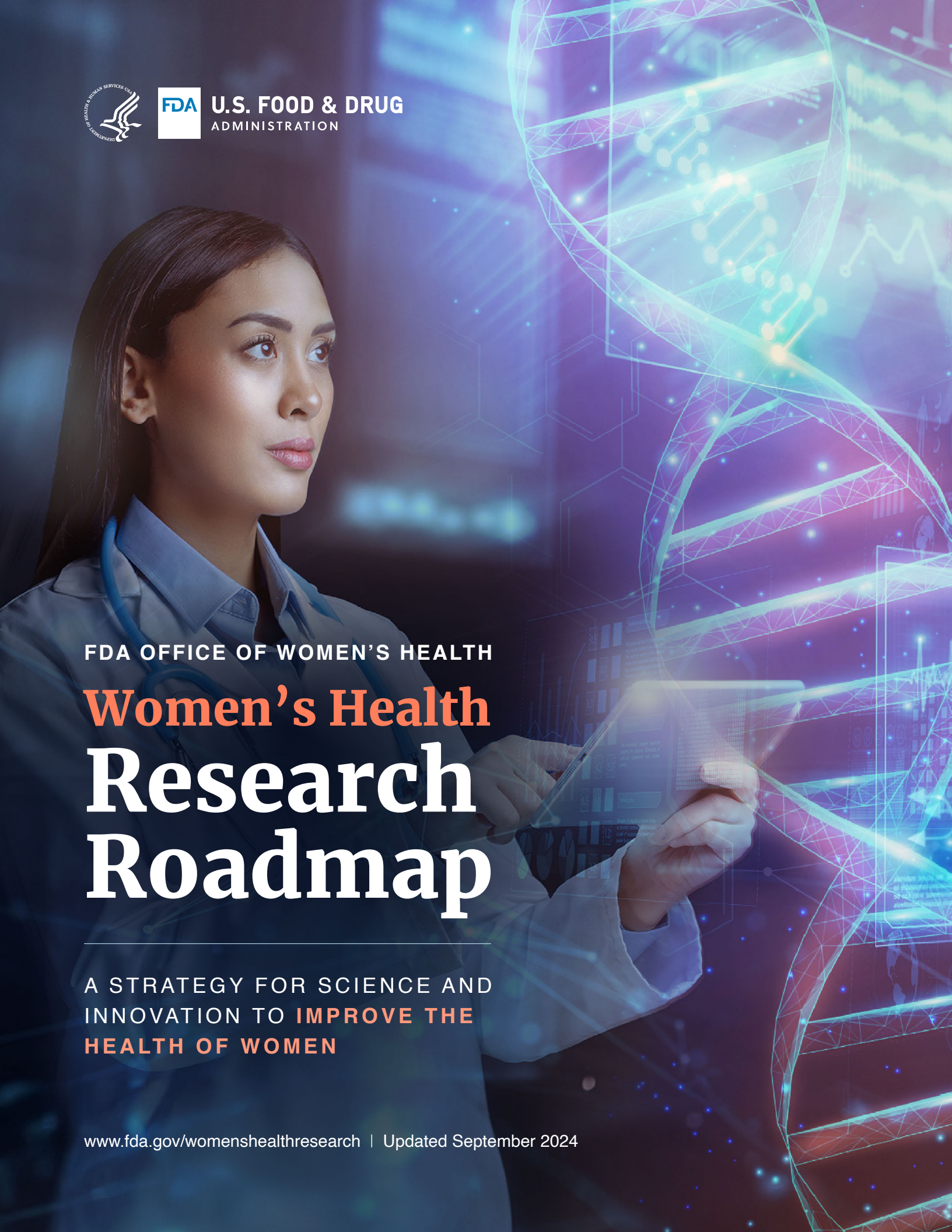


U.S. FOOD & DRUG ADMINISTRATION

FDA OFFICE OF WOMEN'S HEALTH

Women's Health Research Roadmap

A STRATEGY FOR SCIENCE AND INNOVATION TO **IMPROVE THE HEALTH OF WOMEN**

www.fda.gov/womenshealthresearch | Updated September 2024

Executive Summary

The U.S. Food and Drug Administration Office of Women's Health (OWH), part of the Office of the Commissioner, was established in 1994 to protect and advance the health of women and provide leadership on women's health topics within the FDA. OWH supports the FDA's public health and consumer protection mission by leading and coordinating research, policy development, and educational and communication initiatives focused on women's health.

Women and girls make up over half of the U.S. population, yet many women's health topics are understudied. Such topics may include, but are not limited to, conditions unique to women; conditions that impact both women and men, but disproportionately affect women; or conditions that affect women differently. Research gaps are even more prominent for women of color, older women, and women with disabilities. The lack of research and data on women's health contributes to suboptimal medical care and health outcomes for women in the U.S., which, in turn, negatively impacts public health overall. OWH actively works to close these knowledge gaps.

Through the OWH Research Program we have funded over 400 intramural and extramural research projects. This research spurs innovation in scientific knowledge, resulting in the discovery of novel methodologies and technologies, and improvements in the diagnoses and treatment of health conditions that impact women. By promoting collaborative research in mission-critical areas and applying new knowledge to the FDA's review process and regulatory decisions, OWH helps the FDA foster the advancement of research that promotes and protects the health of all people in the U.S.

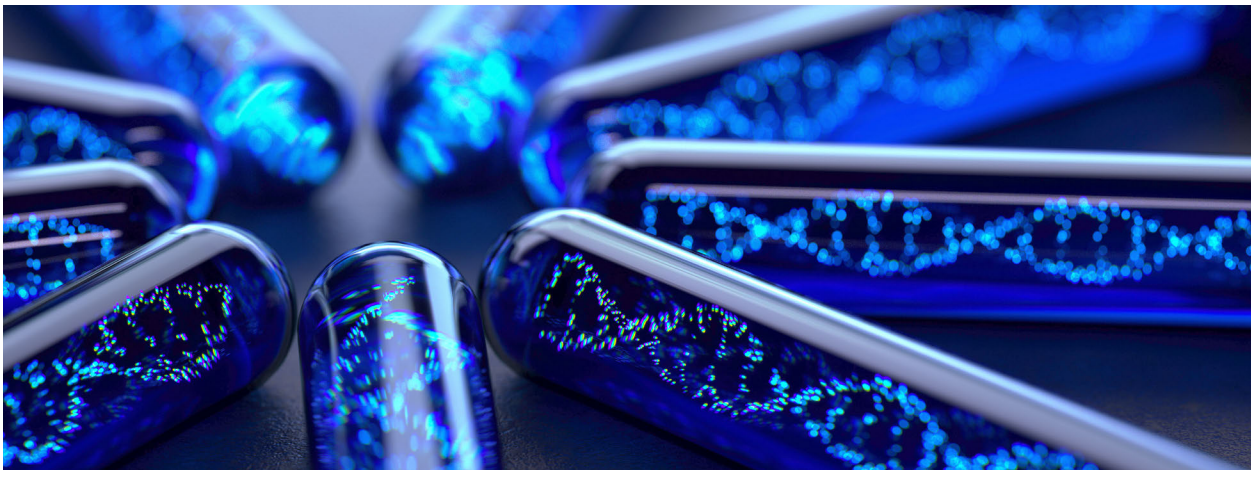
Originally published in 2015, the "Women's Health Research Roadmap" outlines priority areas in which new or further research is needed and serves as a catalyst for research collaborations both internal and external to the FDA. OWH presents our updated "Women's Health Research Roadmap" to reflect current and future women's health needs, priorities, and regulatory research questions. This roadmap provides a science-based framework to support and fund research activities in these seven priority areas essential to OWH's and the FDA's mission:

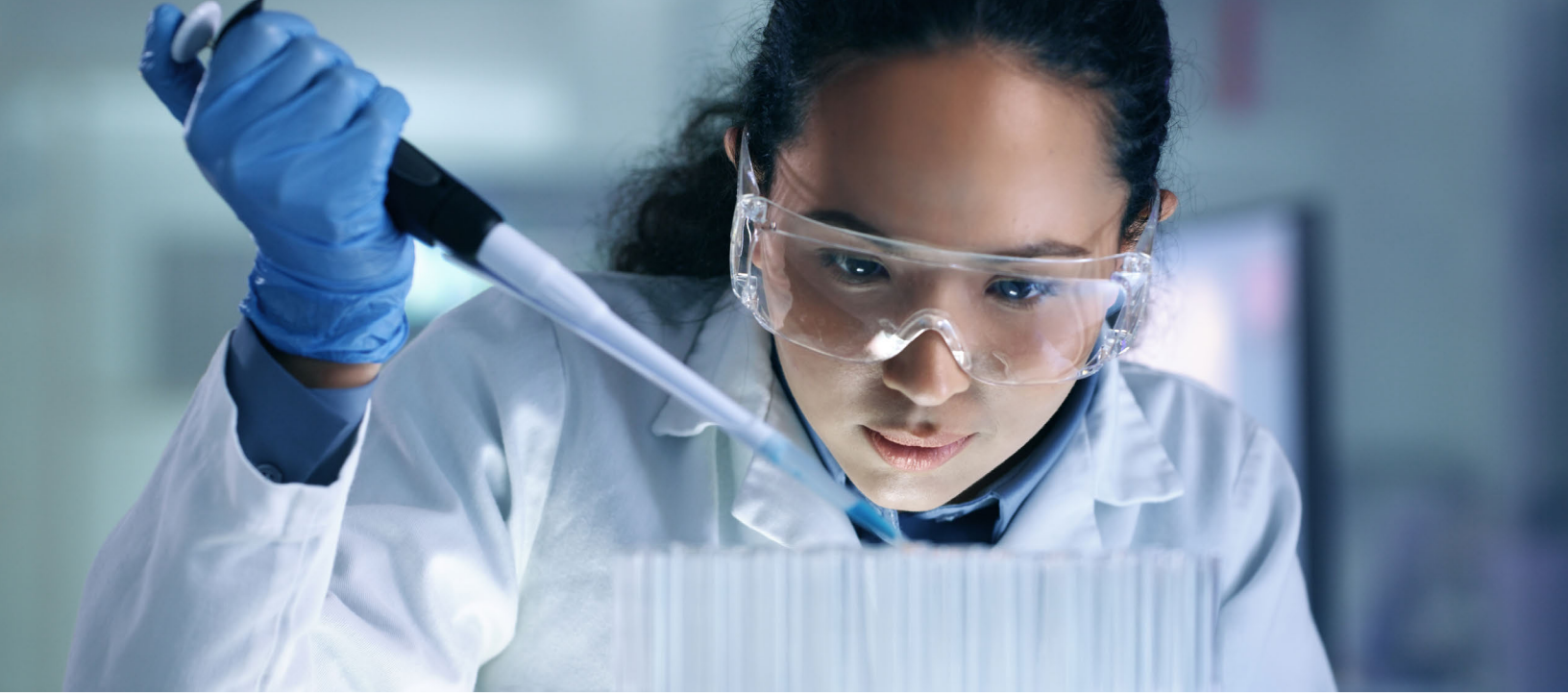
1. Advance Safety and Effectiveness
2. Improve Clinical Study Design and Analyses
3. Advance Biomarker Science
4. Expand Data Sources and Analyses
5. Improve Health Communications
6. Promote Emerging Technologies and Methodologies
7. Combat Emerging Health Threats

In applying this updated roadmap to our work, OWH seeks to fund research that will further expand our understanding of women's health, close gaps in knowledge about FDA-regulated products used by women and inform the FDA's regulatory decisions related to the safety, effectiveness, and security of products.

The purpose of this roadmap is to provide a science-based framework to address women's health research questions and to build women's health science into FDA's research activities. This Roadmap will be used by OWH as a tool to promote women's health research, advance strategic and diverse research investments, maximize research impact, improve collaboration within and external to FDA, and support the translation of research advancements into improved health outcomes.

Researchers should refer to this Roadmap when considering opportunities to collaborate with OWH or when seeking research funding from OWH.





Introduction and Background

FDA's Role and Responsibilities

The U.S. Food and Drug Administration is a science-based, regulatory agency with the core mission of protecting the public health. The FDA regulates over 20,000 prescription drug products and 78 percent of the U.S. food supply. FDA-regulated products account for about 20 cents of every dollar spent by U.S. consumers.[1]

FDA scientists conduct regulatory science, defined as the science of developing new tools, standards, and approaches to assess the safety, effectiveness, quality, and performance of FDA-regulated products.[2] Regulatory science underpins the decisions the FDA makes.

Research at the FDA helps FDA scientists assess the safety, effectiveness, quality, and performance of FDA-regulated products, before and after these products reach U.S. consumers. Such research may help alert the agency and the public to potential safety issues, like product contamination and other problems that may become apparent only after a product enters the marketplace.

FDA research contributes to the advancement of science and technology and promotes innovation in medical product development and food and cosmetic safety.

[1] "FDA At a Glance January 2024", FDA (website), Office of Economics and Analysis, Office of Policy, Legislation and International Affairs, Office of the Commissioner (OC), FDA, U.S. Department of Health and Human Services (HHS), content current as of March 5, 2024, https://www.fda.gov/media/175664/download.

[2] Office of the Chief Scientist, OC, FDA, HHS, 2022: *Advancing Regulatory Science at FDA: Focus Areas of Regulatory Science* (Silver Spring: FDA, 2022), https://www.fda.gov/media/161381/download.

FDA Mission Statement

FDA is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.

FDA is also responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health. FDA also has responsibility for regulating the manufacturing, marketing and distribution of tobacco products to protect the public health and to reduce tobacco use by minors.

FDA also plays a significant role in the Nation's counterterrorism capability. FDA fulfills this responsibility by ensuring the security of the food supply and by fostering development of medical products to respond to deliberate and naturally emerging public health threats.

The Importance of Women's Health Research

Women[3] and girls make up over half of the U.S. population,[4] yet many women's health topics are understudied. The lack of research and data on women's health contributes to suboptimal medical care and health outcomes for women in the U.S., which, in turn, negatively impacts public health overall.[5] According to studies by the Commonwealth Fund, "people in the United States experience the worst health outcomes overall of any high-income nation"[6] and specifically, "women in the United States continue to be disadvantaged by their relatively poorer health status…[and] have the highest rate of maternal mortality among high-income countries."[7]

Some health conditions and diseases can manifest differently based on a person's sex[8]; similarly, a person's sex may affect their response to FDA-regulated products. It is vital

[3] For the purpose of this roadmap, we are using the terms woman/women. We recognize not all biological females identify as women, and not all women are biological females. Although there are differences among FDA centers on the definition of adult, for the purposes of the research that will be supported through the roadmap, we generally define an adult as an individual 17 years or older.

[4] "QuickFacts: United States," United States Census Bureau (website), accessed July 23, 2024, https://www.census.gov/quickfacts/fact/table/US/SEX255223#SEX255223.

[5] Sarah M. Temkin et al., "Perspectives From Advancing National Institutes of Health Research to Inform and Improve the Health of Women: A Conference Summary," *Obstetrics & Gynecology* 140, no. 1 (July 2022): 10-19, https://doi.org/10.1097/AOG.0000000000004821.

[6] Munira Z. Gunja, Evan D. Gumas, and Reginald D. Williams II, *U.S. Health Care from a Global Perspective, 2022: Accelerating Spending, Worsening Outcomes* (New York: The Commonwealth Fund, 2023), https://doi.org/10.26099/8ejy-yc74.

[7] Munira Z. Gunja et al., *What Is the Status of Women's Health and Health Care in the U.S. Compared to Ten Other Countries?* (New York: The Commonwealth Fund, 2018), https://doi.org/10.26099/wy8a-7w13.

[8] The guidance Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial) describes the FDA's current thinking on these terms: sex and gender are distinct terms, with sex defined as a biological construct and gender as a social construct. Sex is the classification of living things, generally as male or female according to their reproductive organs and functions assigned by chromosomal complement. Gender is a person's self-representation as male or female or how that person is responded to by social institutions based on the individual's gender presentation.

to improve our understanding of how to identify sex differences, examine the extent to which such differences may affect patient health, and evaluate how these differences might affect treatment. This information can then be used to guide clinical decisions about the optimal course of action and inform the development of better diagnostic and therapeutic products for women.

Gender may also be an important consideration.[9] Although sex and gender are distinct concepts, they may both influence etiology and presentation of disease, and affect treatment and patient reported outcomes. In the case of pain, for example, sex and gender interact and are interrelated.[10] The perception of pain is influenced by sex hormones and their interaction with endogenous opioid function. Pain is also influenced by gender with regard to coping strategies, which can affect pain responsivity.[11] Therefore, both gender and sex can lead to differences in the way pain is reported, treated, and managed.

More research is needed to understand health throughout a woman's life, including, but not limited to reproductive health events in a woman's life: menstruation, pregnancy, childbirth, lactation, and menopause. For example, it is important to study whether and how hormonal changes affect product performance or clinical outcomes during the menstrual cycle, during pregnancy, and during the transition from pre-menopause to post-menopause. Further, additional research should evaluate how FDA-regulated therapeutic products can be used to reduce maternal morbidity and mortality.

[9] See note 5; Virginia M. Miller, "Why are sex and gender important to basic physiology and translational and individualized medicine?," *American Journal of Physiology-Heart and Circulatory Physiology* 306 no. 6 (March 2014): H781-788, https://doi.org/10.1152/ajpheart.00994.2013.

[10] For more information on the importance of studying sex and gender in clinical research, see "What are Sex & Gender? And why do they matter in health research?," Office of Research on Women's Health, National Institutes of Health, accessed July 24, 2024, https://orwh.od.nih.gov/sex-gender; Nancy Krieger, "Genders, sexes, and health: what are the connections—and why does it matter?," *International Journal of Epidemiology*, 32, no. 4 (August 2003): 652–657, https://doi.org/10.1093/ije/dyg156.

[11] Roger B. Fillingim et al., "Sex, Gender, and Pain: A Review of Recent Clinical and Experimental Findings," *The Journal of Pain* 10, no. 5 (May 2009): 447-85, https://doi.org/10.1016/j.jpain.2008.12.001.

Advances in clinical study designs, such as studies with adaptive and enrichment designs, could help ensure effective use of small samples and sub-population analyses. New methods, processes, and tools, including modeling (e.g., *in vitro* and computational modeling) and other novel technologies, can help evaluate medical device designs, predict toxicity, assess the safety and effectiveness of FDA-regulated products, and guide medication dosing for women. Biomarkers,[12] surrogate endpoints, patient reported outcomes, and other tools are increasingly being used in medical product development and in the clinic to help understand disease, therapy, and patient response to therapy. Advances in the science of biomarkers could help improve our understanding of the molecular underpinnings of disease in women, leading to improvements in personalized, or precision medicine[13]. Strengthening our understanding in these areas will contribute to FDA's ability to carefully evaluate how medical products work in diverse populations of women.[14]

While it is well known that there are differences in the course and impact of health conditions and diseases based on sex,[15] research on sex differences and other women's health topics remains underfunded. A 2021 study assessed research funding across 74 diseases; 14 of the 15 underfunded research areas were female dominant diseases.[16] The lack of funding devoted to women's health research results in significant knowledge gaps in conditions that solely or disproportionately affect women, ranging from migraines to endometriosis.

The FDA has a long history of assessing the possibility of differences across demographic groups in the safety and effectiveness of the products we regulate. This stipulation begins early in the product development process. Medical product developers are expected to include animals of both sexes in preclinical studies of

[12] FDA-NIH Biomarker Working Group, *BEST (Biomarkers, EndpointS, and other Tools) Resource*, (Silver Spring: FDA; Bethesda: National Institutes of Health (NIH), 2021), https://www.ncbi.nlm.nih.gov/books/NBK326791/; Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER), FDA, HHS, "Qualification Process for Drug Development Tools Guidance for Industry and FDA Staff (Final)" (Silver Spring: FDA, 2020), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/qualification-process-drug-development-tools-guidance-industry-and-fda-staff. There are various types of biomarkers. Examples include diagnostic biomarkers to identify the presence or absence of a specific physiological or pathophysiological state or disease; prognostic biomarkers to help identify and categorize patients by degree of risk for disease occurrence or progression or to inform about the natural history of a disorder in a particular patient in the absence of a therapeutic intervention; and predictive biomarkers to help identify and categorize patients by their likelihood of response to a particular treatment and to help identify a subpopulation likely to respond to a treatment intervention in a particular way.

[13] "Precision Medicine," In Vitro Diagnostics, FDA, HHS, content current as of September 27, 2018, https://www.fda.gov/medical-devices/in-vitro-diagnostics/precision-medicine. Precision medicine, sometimes known as "personalized medicine," is an innovative approach to tailoring disease prevention and treatment that takes into account differences in people's genes, environments, and lifestyles.

[14] The intent of this roadmap is to be inclusive of all women. The phrase "diverse populations of women" is used in this document to include women with a diverse array of co-morbidities as well as those from diverse backgrounds, diverse racial and ethnic populations, diverse ages, and diverse life stages (e.g., those of reproductive potential, those who are pregnant or lactating, and those who are menopausal or postmenopausal).

[15] Institute of Medicine, Exploring the Biological Contributions to Human Health: Does Sex Matter? (Washington, DC: The National Academies Press, 2001), https://doi.org/10.17226/10028.

[16] Arthur A. Mirin, "Gender Disparity in the Funding of Diseases by the U.S. National Institutes of Health," *Journal of Women's Health* 30, no. 7 (July 2021): 956-963, https://doi.org/10.1089/jwh.2020.8682.

candidate drugs or biologics if the medical product will be used in both sexes upon approval.[17] For most drugs, both sexes should be included in clinical trials in numbers adequate to allow detection of clinically significant sex-related differences in drug response.[18]

Historically, women have been underrepresented in clinical and noninterventional studies of medical products.[19] Over the years, the FDA has promoted greater participation and representation of women in clinical studies not only to accurately assess the safety and effectiveness of drugs and medical devices, but also to bridge knowledge gaps to advance women's health. Yet women continue to be underrepresented in many clinical studies. A 2022 study of clinical trials conducted between 2016-19 revealed that in clinical trials with adult cardiovascular, psychiatric, and cancer endpoints, 41.2% of participants were females despite comprising more than 50% of the patients/disease population in each area.[20] Additionally, in a decadal review of drug approvals from 2005 to 2015, FDA researchers found that women were underrepresented in trials of cardiovascular medications for heart failure, coronary artery disease, and acute coronary syndrome/myocardial infarction—making up less than 29% of trial participants despite comprising more than 43% of the disease populations.[21] Further, because pregnant and lactating women are usually excluded from pivotal clinical trials, there is a lack of knowledge of medication safety and effectiveness in these patients.[22]

In human studies, FDA regulations require the presentation of demographic data on age, gender and race[23] in marketing applications to help identify important information about possible differences in the safety or effectiveness of drugs across demographic subgroups. The FDA has also issued guidance for industry and FDA staff on the study and evaluation of sex-specific data in medical device clinical studies.[24]

[17] "Advancing Alternative Methods at FDA," About Science & Research at FDA, FDA, HHS, content current as of November 14, 2023, https://www.fda.gov/science-research/about-science-research-fda/advancing-alternative-methods-fda. Note that FDA is committed to reducing the number of animals used in testing or eliminating their use all together to the extent possible.

[18] CBER and CDER, FDA, HHS, "Enhancing the Diversity of Clinical Trial Populations Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry (Final)," (Silver Spring: FDA, 2020), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial.

[19] Linda Ann Sherman, Robert Temple, and Ruth B. Merkatz, "Women in clinical trials: an FDA perspective." *Science* 269, no. 5225 (1995): 793-795. https://www.science.org/doi/epdf/10.1126/science.7638593

[20] Sosinsky, et al., "Enrollment of Female Participants," 115.

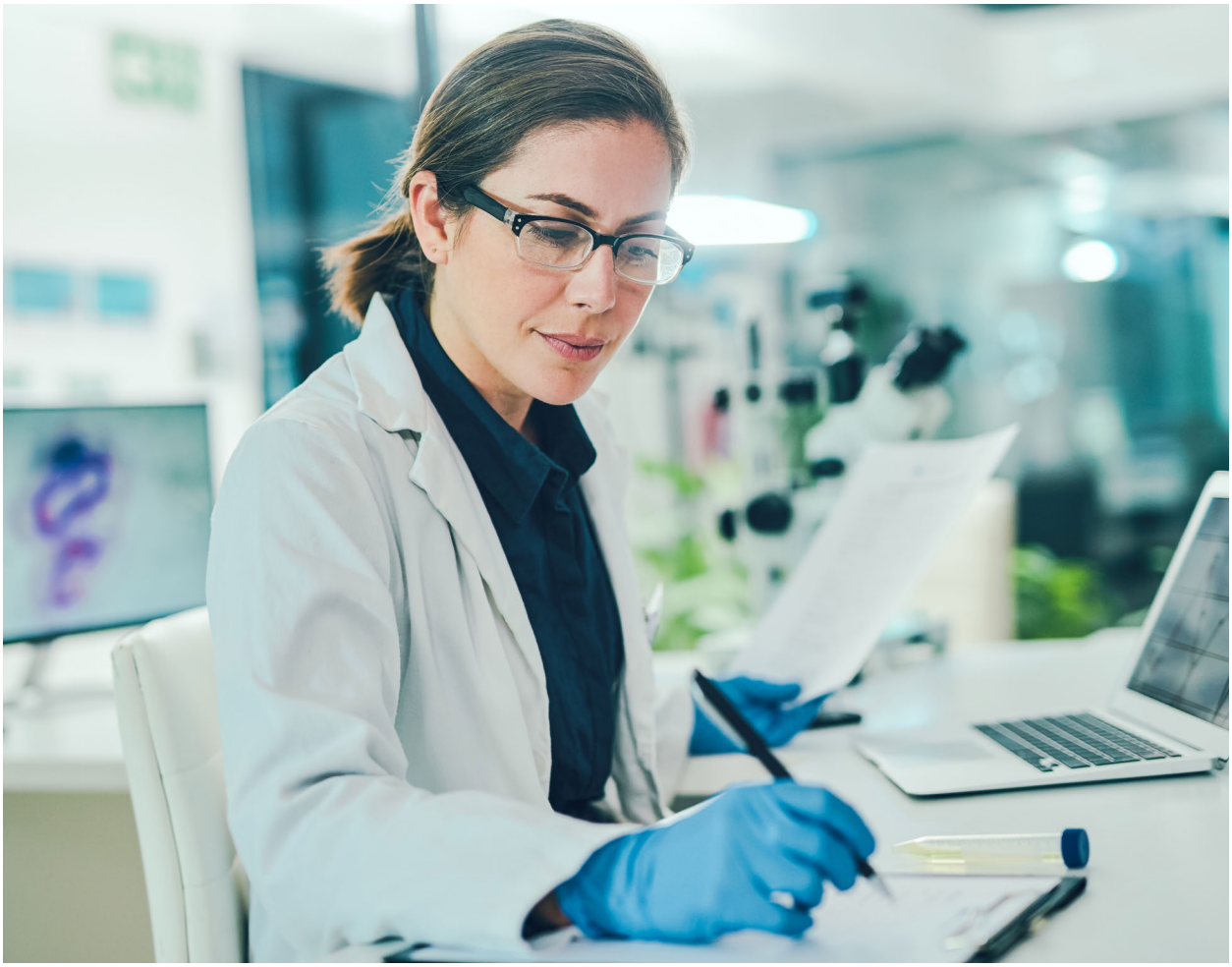
[21] Pamela E. Scott et al., "Participation of Women in Clinical Trials Supporting FDA Approval of Cardiovascular Drugs," *Journal of the American College of Cardiology* 71, no. 18 (May 2018): 1960-1969, https://doi.org/10.1016/j.jacc.2018.02.070.

[22] CDER and CBER, FDA, HHS, "Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials (Draft)," (Silver Spring: FDA, 2018), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pregnant-women-scientific-and-ethical-considerations-inclusion-clinical-trials; Lisa Thiele et al., "Gaps in Evidence-based Medicine: Underrepresented Populations Still Excluded from Research Trials Following 2018 Recommendations from the Health and Human Services Task Force on Research Specific to Pregnant Women and Lactating Women," *American Journal of Obstetrics and Gynecology* 227, no. 6 (December 2022): 908-909, https://doi.org/10.1016/j.ajog.2022.07.009.

[23] "Content and Format of an NDA," 21 C. F. R. 314.50, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=314.50.

[24] CDRH, FDA, HHS, "Evaluation of Sex-Specific Data in Medical Device Clinical Studies - Guidance for Industry and

Outside of the FDA, Congress has shown an increased interest in inclusion of women in research studies. For example, the Food and Drug Omnibus Reform Act of 2022 (FDORA) generally requires sponsors to submit diversity action plans to the FDA for certain clinical investigations of new drugs and investigational devices, which must include, among other things, the sponsor's goals for enrollment. FDORA further requires the FDA to update or issue guidance relating to the format and content of such diversity action plans pertaining to the sponsor's goals for clinical study enrollment, disaggregated by sex, among other things.[25]



Food and Drug Administration Staff (Final)," (Silver Spring: FDA, 2014), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/evaluation-sex-specific-data-medical-device-clinical-studies-guidance-industry-and-food-and-drug; CDER, FDA, HHS, "CDER Guidance Agenda New, Revised Draft and Immediately in Effect Guidances Planned for Publication in Calendar Year 2024," (Silver Spring: FDA, 2024), https://www.fda.gov/media/134778/download

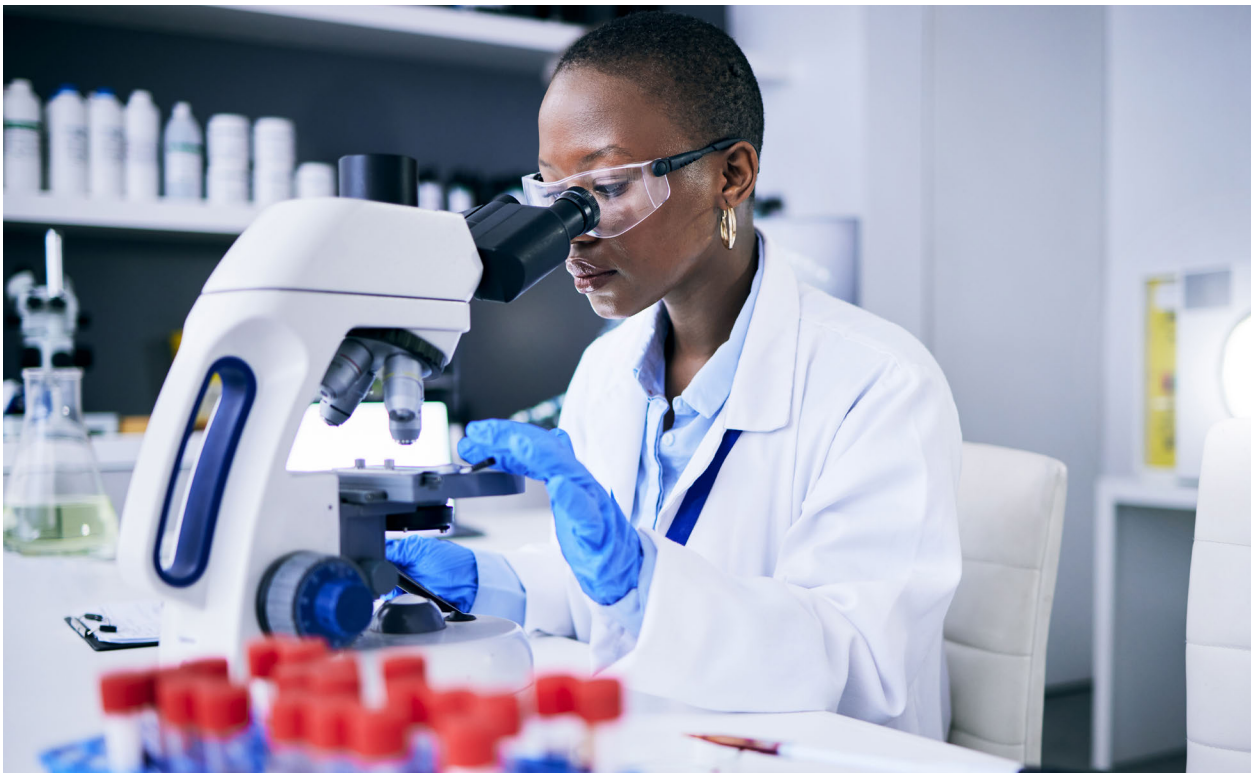
[25] Consolidated Appropriations Act, 2023, Pub. L. No. 117-328, 136 Stat. 4457 (2022), https://www.congress.gov/117/plaws/publ328/PLAW-117publ328.pdf; OCE, CBER, CDER, CDRH, OC/OMHHE, OC/OWH, FDA, HHS, "Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies (Draft)," (Silver Spring: FDA, 2024), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/diversity-action-plans-improve-enrollment-participants-underrepresented-populations-clinical-studies.

FDA's Office of Women's Health Research Program

The FDA's Office of Women's Health (OWH) was established in 1994 to provide leadership on women's health topics within the FDA. OWH's mission is to help protect and advance the health of women through policy, science, education, and outreach; advocate for inclusion of women in clinical studies and for the analysis of data for sex differences; and increase the scientific knowledge of women's health and sex differences through advanced professional training and education.[26]

In 1994, OWH established a research program to:

- Advance the evaluation of sex differences in the safety and effectiveness of FDA-regulated products.
- Conduct research on health conditions and diseases that solely or disproportionately affect women.
- Track and analyze data regarding the participation of women in clinical research.
- Advance scientific knowledge of women's health through professional training and education.



[26] "What We Do, From the FDA Office of Women's Health," Women's Health, FDA, HHS, content current as of December 28, 2023, https://www.fda.gov/consumers/about-owh/what-we-do.

Through the OWH Research Program, we have funded over 400 intramural and extramural research projects. OWH-funded projects carried out by FDA centers, by contracted academic researchers, and in collaboration with academic institutions have advanced the understanding of sex differences, examined health conditions unique to women, and evaluated data to improve women's health. Projects include, identifying breast cancer biomarkers, researching maternal health topics, assessing sex differences in response to medical devices, evaluating adverse events among women related to drugs for cardiovascular disease, assessing sex differences in drug interactions of HIV therapeutics, evaluating the safety of dietary supplements, investigating other health conditions and research areas, and many others

This research has contributed to safety labeling changes for medical products, provided data to support product market withdrawal, contributed to new guidance for industry on product development, promoted data standardization for vaccine clinical data, supported standards for breast cancer MRI imaging, and provided evidence-based support for products recommended for use during pregnancy.[27] OWH-funded research also serves as the foundation for the development and expansion of other women's health research activities, including, for example, the OWH Research Fellowship, which helps promote innovative research to advance the study of women's health in mission-critical areas.

OWH supports the FDA's public health and consumer protection mission by leading and coordinating research, policy development, and educational and communication initiatives addressing women's health. As described in the box below, OWH's Research Program leads and supports a variety of activities through intramural research grants, FDA research program collaborations, external research collaborations, and OWH-initiated research, workshops, and training.

By promoting collaborative research in mission critical areas, developing tools, helping to develop knowledge that can then be used in the FDA's regulatory work, and strategically coordinating the findings so they inform regulatory and policy decisions, OWH's research program helps the FDA foster the advancement of research that promotes and protects the health of all Americans.

[27] Merina Elahi et al., "The Food and Drug Administration Office of Women's Health: Impact of Science on Regulatory Policy: An Update," *Journal of Women's Health* 25, No. 3 (March 2016): 222-234, https://doi.org/10.1089/jwh.2015.5671.

Office of Women's Health Research Program

Intramural Research Grants

- **Competitive Grants:** FDA-scientists respond to an annual call for proposals from OWH to compete for grant funding through a rigorous peer-review process.
- **Special Funding Initiatives:** Funding under this mechanism may be awarded to FDA scientists, after a rigorous peer-review process, in response to emerging and pressing women's health priorities.

ORISE Fellowship Funding

This mechanism is offered to support the various competitive grants and special funding initiatives awarded to FDA scientists, after a rigorous peer-review process, and provides practical training for recent undergraduates and graduate degrees earned in science, technology, engineering, and math (STEM).

OWH Research Fellowship Program

OWH Research Fellowship Program is designed to promote innovative research and collaboration between center investigators and OWH within FDA's intramural research environment to facilitate the progress of women's health studies.

FDA Research Program Collaborations

FDA product centers and offices directly support women's health research through grants, cooperative agreements, or contracts. OWH also collaborates with other FDA research programs to better integrate women's health research questions into other FDA research activities.

External Research Collaborations

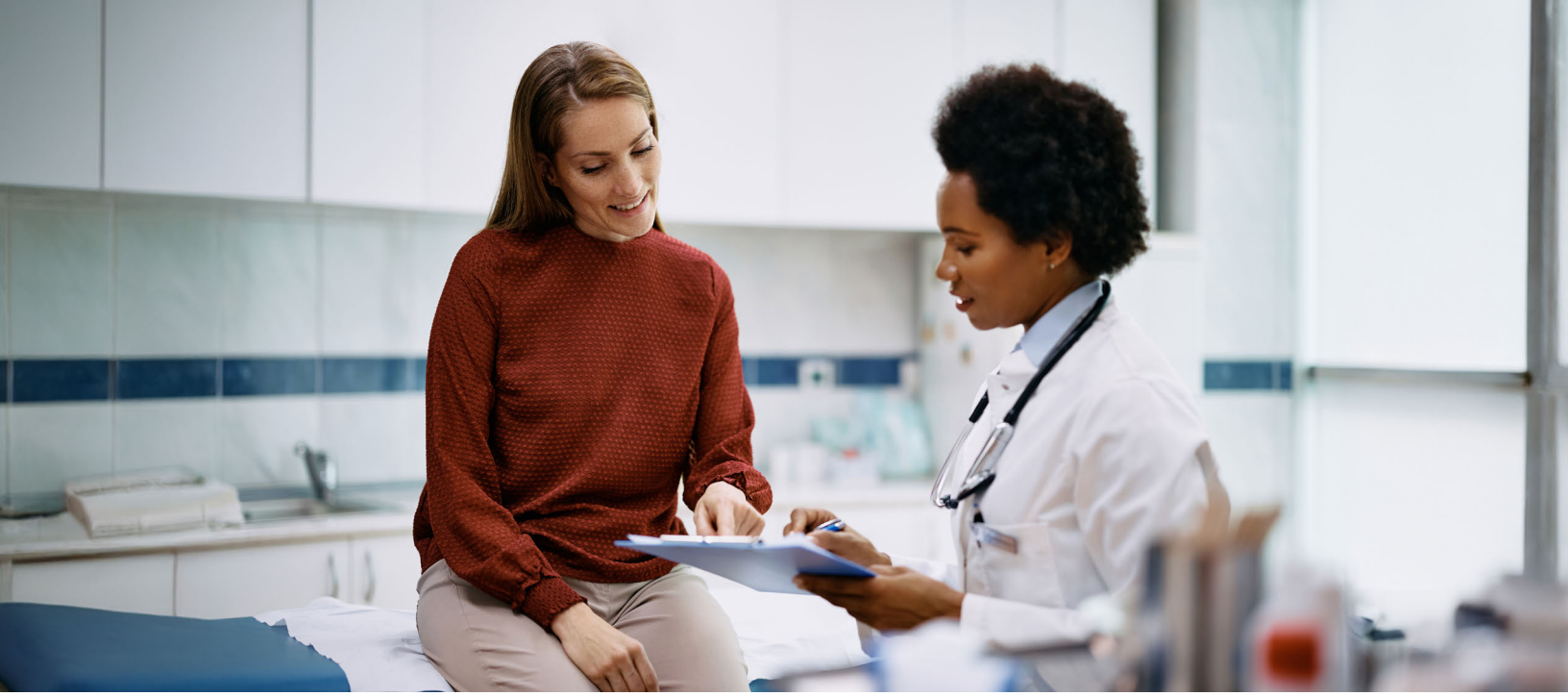
Collaborations with external partners to help FDA leverage all available technologies, expertise, and resources when addressing complex women's health research questions. There are two mechanisms for funding extramural research: (1) Centers of Excellence in Regulatory Science and Innovation (CERSI) and (2) Broad Agency Announcements (BAA).

OWH Workshops and Training

These activities include scientific workshops, trainings, and curriculum development for researchers and health professionals designed to advance the understanding of women's health and sex differences.

OWH-Initiated Research

OWH conducts staff-led research and data analysis projects to advance women's health in areas of unmet need. OWH manuscripts are published in peer-reviewed scientific and medical journals, and OWH staff present findings at conferences around the country.



Women's Health Research Roadmap

The purpose of this roadmap is to provide a science-based framework to address women's health research questions, including investigating sex differences throughout the product development process from basic science through clinical research, and to build women's health research into the FDA's scientific activities. The priority areas described in the roadmap will allow OWH to make science-driven funding decisions that are aligned with the FDA's research priorities, focusing on gaps in knowledge about FDA-regulated products used by women, and that are directly relevant to the FDA as it makes regulatory decisions related to the safety, effectiveness, and security of FDA-regulated products used by women. The roadmap is designed to serve as a catalyst for future collaborations intended to help protect and promote the health of women through advancements in policy, science, outreach, and education. Because the roadmap is a highly valued resource, it was designated an action item in the 2014 FDA Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data[28] and remains a key component in the FDA's current activities related to advancing women's health

Progress

Originally published in 2015, the roadmap outlined priority areas in which new or further research was needed. The roadmap was built on knowledge gained from previously funded research and has been used to assist OWH in coordinating new health research

[28] FDA, HHS, *FDA Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data* (Silver Spring: FDA, 2014), https://www.fda.gov/media/89307/download. The Action Plan was provided for in Section 907 of the Food and Drug Administration Safety and Innovation Act (FDASIA).

activities, including collaborative projects with other FDA research programs and external partners. Since it was first published, the roadmap has served as a catalyst for enhanced research collaboration, new partnerships, internal alignment, and public transparency.

Specifically, OWH has:

- **Enhanced Intra-Agency Collaboration** by engaging with other FDA centers and offices on cross-discipline projects that advance women's health.
- **Established a Women's Health Research Steering Committee (WHRSC)** that continues to serve as a scientific expert resource, engaged and partnered with OWH on revising the roadmap, and driven the research agenda pertaining to women's health at the FDA.
- **Implemented Mechanisms to Facilitate Women's Health Research,** such as the OWH Research Fellowship and Centers of Excellence in Regulatory Science and Innovation (CERSI) collaborations as well as through information sessions and workshops on OWH's work, partnership opportunities, and project findings for internal and external stakeholders.
- **Improved General Funding Metrics** by refining research outcomes and measures of scientific and regulatory impact.

OWH will continue to build on these accomplishments and expand our work in these areas as they are central to women's health research.

Roadmap Updates

We are presenting this update to the "2015 Women's Health Research Roadmap" to better reflect present and future women's health needs, priorities, and regulatory research questions. OWH reviewed and updated the 2015 roadmap using a three-pronged strategy:

1. **OWH Federal Register Notice (FRN)**
   In July 2020 OWH published a FRN requesting public comment from stakeholders interested in informing strategic priorities for OWH. We considered these comments as we updated the roadmap.
2. **FDA Center and Office Priorities**
   WHRSC members provided detailed input on women's health research areas and regulatory priorities that were of importance to their respective centers and offices.
3. **OWH Portfolio Analysis**
   OWH performed a gap analysis of the OWH research portfolio from 2012 to 2024 to identify understudied women's health research areas.

Based on the information gained through this process, OWH outlined additional research areas considered to be high priority which were not already included in the roadmap. In this updated roadmap, OWH combined two priority areas—Novel Modeling and Simulation Approaches with Promoting Emerging Technologies—and added an additional priority area focused on Combating Emerging Threats. The updated roadmap was vetted by WHRSC members, and FDA centers and offices.

Priority Areas

OWH, in collaboration with the WHRSC, identified seven priority areas in which new or further research is essential to OWH's and the FDA's mission. Below is information on OWH's research goals for each priority area.

1. Advance Safety and Effectiveness

- Explore how sex differences may affect regulatory decision-making around medical product safety and effectiveness or play a role in the use of other regulated products (e.g., cosmetics).
- Explore the possible effects of FDA-regulated products on diverse populations of women. OWH is interested in funding research where data is disaggregated and analyzed not only by sex, but also by age, race, and ethnicity,[29] and where gender, which is also an important factor in clinical research, is included in data collection when appropriate.[30]
- Expand the FDA's capacity to effectively evaluate FDA-regulated products used by women throughout all life and disease stages.

2. Improve Clinical Study Design and Analyses

- Develop and promote use of better methodologies for identifying and evaluating how sex and gender may influence the safety and effectiveness of FDA-regulated products.
- Identify and evaluate best practices for recruitment and retention of diverse populations of women in clinical studies.
- Include considerations for social and behavioral research studies (e.g., patient-reported outcomes) which can enhance the effectiveness and safe use of FDA-regulated therapeutic products.

[29] "Food and Drug Administration Safety and Innovation Act (FDASIA)," Laws Enforced by FDA, FDA, HHS, content current as of March 28, 2018, https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/food-and-drug-administration-safety-and-innovation-act-fdasia.

[30] CDER, CDRH, and CBER, FDA, HHS, "Collection of Race and Ethnicity Data in Clinical Trials Guidance for Industry and Food and Drug Administration Staff (Final)," (Silver Spring: FDA, 2016), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/collection-race-and-ethnicity-data-clinical-trials.

3. Advance Biomarker Science

- Identify, develop, and evaluate biomarkers in nonclinical and clinical studies that can better measure and predict the safety and effectiveness of FDA-regulated products in women.
- Expand FDA's knowledge of diagnostic, prognostic, and predictive biomarkers that can detect and predict the severity and progression of conditions in women and identify patients at risk for adverse events.

4. Expand Data Sources and Analyses

- Provide the FDA with the tools needed to integrate and interpret diverse data to support evaluation of safety and effectiveness of FDA-regulated products used by women.
- Provide additional tools to help identify adverse events in women and support changes in practice patterns.

5. Improve Health Communications

- Identify methods to create, disseminate, and maximize the use of effective health communication materials for diverse populations of women.
- Promote access to truthful and non-misleading information regarding the benefit and risk of FDA-regulated products and ensure the information is tailored to women's needs.
- Support product labeling and other FDA communications for health care professionals who will benefit from clear and readily available prescribing, dispensing, product use, and safety information.

6. Promote Emerging Technologies and Methodologies

- Develop and adopt new methods and tools for evaluating new technologies that consider sex and gender differences.
- Enhance the FDA's ability to evaluate innovative products and novel technologies to efficiently integrate beneficial new products into mainstream health care for women.
- Enrich the FDA's knowledge and application of emerging technologies, methodologies, and tools to address women's health concerns, specifically in understudied areas.
- Advance the understanding of the possible effects of sex differences on the use of these new technologies and scientific fields.

7. Combat Emerging Health Threats

- Develop tools to identify public health threats, prevent them from becoming crises, and promote public health security, with a focus on women.
- Support and promote the inclusion of women and evaluations of sex differences in the development of medical countermeasures.[31]

In the following sections, each research priority area is discussed in more detail, noting how the research would support FDA activities and advance public health. A few examples of specific research objectives are also provided.

PRIORITY AREA 1: ADVANCE SAFETY AND EFFECTIVENESS

Advance the safety and effectiveness of FDA-regulated therapeutic and diagnostic products used by women.

Proposed research in this priority area should take a comprehensive look at the diseases and health conditions that solely or disproportionately affect women, and the areas in which additional research is needed to advance our understanding of women's health. It should focus on research areas of unmet medical need and scientific gaps related to FDA-regulated products, and other knowledge gaps in women's health.

Research in this area should aim to:

- Explore how sex differences may affect medical product safety and effectiveness or play a role in the use of other FDA-regulated products.
- Explore the possible effects of FDA-regulated products on diverse populations of women.
- Expand the FDA's capacity to evaluate FDA-regulated products used by women throughout all life and disease stages.

The FDA will use the results of this research to advance the understanding of disease presentation and manifestation in women, to elucidate the mechanisms of action of regulated products, and to evaluate women's responses to these products.

[31] "What are Medical Countermeasures? Medical Countermeasures, or MCMs, Are FDA-regulated Products (Biologics, Drugs, Devices) That May Be Used in the Event of a Potential Public Health Emergency," Emergency Preparedness and Response, FDA, HHS, content current as of June 11, 2024, https://www.fda.gov/emergency-preparedness-and-response/about-mcmi/what-are-medical-countermeasures.

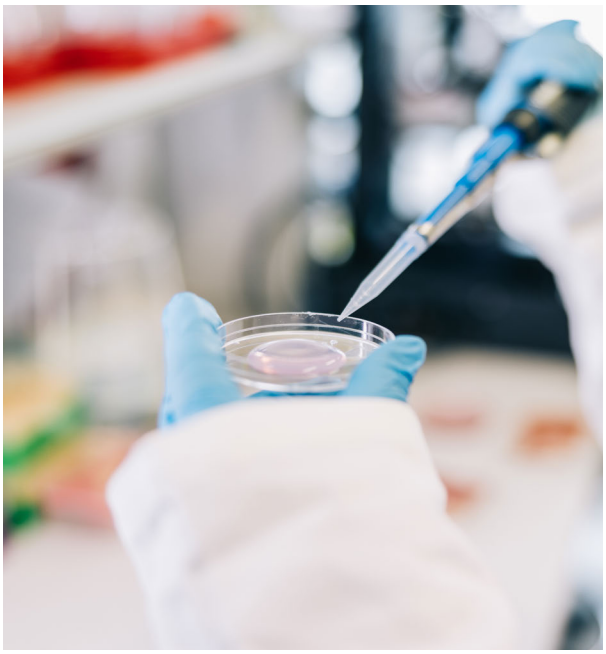
Potential health impacts of this research include gaining a better understanding of diseases in specific populations of women (e.g., older[32] or pregnant women), which should enhance the ability of patients and their health care providers to make evidence-based treatment decisions. Advances in the science of women's health will improve and enhance women's health overall.

Objectives

1.1 Advance our understanding of women's health, including diseases and conditions that primarily affect women's lives. Topics may include breast health, reproductive health, and obstetric and gynecological health.

1.2 Expand evaluation of regulated products for areas in which additional research is needed to advance our understanding of disease prevention, presentation, manifestation, and treatment in women that may be different from men; promote innovation in product development; or address disparities affecting women. Topics may include, but are not limited to, major causes of morbidity and mortality such as:

- Autoimmune disease
- Cancer
- Cardiovascular disease
- Childbirth and pregnancy
- Diabetes
- HIV and AIDS
- Long COVID
- Lung disease
- Mental health (including maternal mental health)
- Neurological conditions
- Obesity
- Osteopenia/Osteoporosis
- Substance use disorder



1.3 Improve our understanding of the apparent role of sex-correlated co-morbidities, concomitant medications, nicotine and tobacco products, other subgroup differences (e.g., age, race, ethnicity, body composition, physiology), and metabolism of drugs and biologics on the safety and effectiveness of FDA-regulated products.

[32] For purposes of this roadmap, generally considered to be persons who are 65 years old and older.

1.4 Evaluate the role of sex hormones on the effectiveness and safety of medical products.

1.5 Develop tools and methods in support of development of diagnostics and therapeutics targeting women, including, but not limited to:

- Tools and methods to evaluate innovative, new devices and diagnostics specifically designed for use in women (e.g., gynecological devices).
- Tools and methods to enhance the evaluation of devices used in both men and women to take into consideration sex differences, such as organ size, anatomy, and physiology, as well as gender differences that may affect device performance.

1.6 Enhance our understanding of how FDA-regulated products work in diverse populations of women, including, but not limited to these examples:

- Older women—Identify sex-specific biomarkers for disease progression and treatment outcomes in women, including older women with comorbid conditions and those who use multiple therapeutic agents.
- Pre- and post-menopausal women—Investigate how the effects of hormonal changes and reproductive transition in pre- and post-menopausal women may affect the safety and effectiveness of FDA-regulated products.
- Pregnant women—Enhance our understanding of the safety and effectiveness of FDA-regulated therapeutic products used during pregnancy and postpartum period.
- Lactating women—Evaluate the safety of FDA-regulated products that may be transferred into breast milk, including drugs; biologics; potential toxicants, including from nicotine, tobacco and tobacco products (such as e-cigarettes, tobacco smoke or other secondhand toxin exposures); and materials used in manufacturing medical devices.
- Women of reproductive potential—Increase the body of knowledge on fertility preservation in women with cancer and the mitigation of hormonal dysfunction related to FDA-regulated products. Explore approaches to better support women seeking to become pregnant and women seeking to prevent pregnancy.

PRIORITY AREA 2: IMPROVE CLINICAL STUDY DESIGN AND ANALYSES

Improve clinical study design, conduct, and analysis to better identify and evaluate sex differences and gender influences related to FDA-regulated products.

This priority area focuses on improving clinical studies supporting FDA-regulated products to better evaluate sex differences—and gender differences, as appropriate—and to improve the safety and effectiveness of FDA-regulated therapeutic products for conditions that primarily affect women. Sex and gender may each influence etiology and presentation of disease, affect treatment and patient-reported outcomes, and may be an important consideration for certain endpoints.[33] One relevant example of the influence of physiological differences between males and females on drug pharmacokinetics (PK) is the sedative-hypnotic drug, zolpidem. Originally approved for short-term treatment of insomnia in 1992, zolpidem's labeling recommended an adult dose of 10 mg immediately before bedtime, which was to be individualized for each patient.[34] After careful consideration of the post-market reports, new PK and pharmacodynamic data, and new driving simulation data, the FDA required changes to zolpidem's labeling in 2013 after stating that women appear to be more susceptible to the risk of next-morning impairment because they eliminate zolpidem more slowly than men.[35]

The diagnosis and management of heart diseases provides a relevant example of the influence of gender. Compared to men, women are 20% more likely to develop heart failure or to die within five years after their first severe heart attack.[36] Contributing gender influences include: women are seen less frequently in the hospital by a cardiovascular specialist; fewer women are prescribed medications, such as beta blockers or cholesterol-lowering drugs; and women also have slightly lower rates of revascularization procedures to restore blood flow, such as surgical angioplasty.[37]

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[33] Virginia M. Miller, "Why are sex and gender important to basic physiology and translational and individualized medicine?," *American Journal of Physiology-Heart and Circulatory Physiology* 306 no. 6 (March 2014): H781-788, https://doi.org/10.1152/ajpheart.00994.2013.

[34] "Zolpidem NDA 19908"(Silver Spring: FDA, 1991), https://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/019908_S000_BIOR.pdf.

[35] "FDA Drug Safety Communication: FDA Approves New Label Changes and Dosing for Zolpidem Products and a Recommendation to Avoid Driving the Day After Using Ambien CR," Drug Safety and Availability, FDA, HHS, first published May 14, 2013, https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-approves-new-label-changes-and-dosing-zolpidem-products-and; "FDA Drug Safety Communication: Risk of Next-morning Impairment After Use of Insomnia Drugs," Drug Safety and Availability, FDA, HHS, first published January 10, 2013, https://wayback.archive-it.org/7993/20170404172106/https://www.fda.gov/Drugs/DrugSafety/ucm334033.htm. The term "women" was used in the drug safety communication and label.

[36] Justin A. Ezekowitz et al., "Is There a Sex Gap in Surviving an Acute Coronary Syndrome or Subsequent Development of Heart Failure?," *Circulation* 142, no. 23 (December 2020): 2231-2239, https://doi.org/10.1161/CIRCULATIONAHA.120.048015.

[37] Ezekowitz et al., "Is There a Sex Gap?," 142; T. Lopez Sobrino et al., "Women Take Longer to Seek Help When Suffering a STEMI," *European Heart Journal: Acute Cardiovascular Care* 12, no. S1 (May 2023): i127-i128, https://doi.org/10.1093/ehjacc/zuad036.090.

Historically, women were often excluded from clinical studies supporting product development. Despite the progress in inclusion of women, more research and improvements to clinical study designs are needed. These studies may be directed at facilitating the identification of sex differences, gaining a better understanding of the biological basis for sex differences, and understanding how a person's sex and gender can affect the safety and effectiveness of regulated products. Work in this priority area will complement other efforts to overcome any remaining barriers to including women in clinical research. Furthermore, increasing the recruitment and retention of diverse populations of women in clinical studies will help improve the safety and effectiveness of FDA-regulated therapeutic products used by women.

Research in this area should aim to:

- Develop and promote use of better methodologies for identifying and evaluating sex differences and gender influences on the safety and effectiveness of FDA-regulated products.
- Identify and evaluate best practices for recruitment and retention of diverse populations of women in clinical studies.
- Include considerations for social and behavioral research studies (e.g., patient-reported outcomes) which can enhance the effectiveness and safe use of FDA-regulated therapeutic products.[38]

Objectives

2.1 Identify and evaluate best practices for the recruitment and retention (e.g., new strategies, approaches) of diverse populations of women in clinical studies.

2.2 Develop and promote the novel use of clinical study designs (e.g., adaptive designs, observational studies, registries) and statistical methods (Bayesian methods, meta-analyses) to evaluate sex and gender differences and perform other subgroup analyses regarding the safety and effectiveness of FDA-regulated products, especially those used for health conditions that solely or predominantly affect women. Considerations include, but are not limited to:

- Determining how to incorporate and interpret data from women in clinical studies conducted in other countries with demographic profiles different from those in the U.S., especially when U.S. data are unavailable or incomplete.
- Developing analytical methods for interpreting and using data on sex and gender differences from studies with small sample sizes.
- Determining how best to incorporate sex and gender data from electronic health records with other study data when evaluating pragmatic clinical trials.[39]

[38] FDA, HHS, *A Strategic Plan: Advancing Regulatory Science at FDA* (Silver Spring: FDA, 2011), https://www.fda.gov/media/81109/download. See strategic priority # 8: Strengthen Social and Behavioral Science to Help Consumers and Professionals Make Informed Decisions about Regulated Products.

[39] For purposes of this roadmap, pragmatic trials or studies refer to trials or studies carried out as part of routine

2.3 Identify appropriate endpoints and outcome measures, including patient-reported outcome measures, for diseases or medical products that may affect women differently from men (e.g., certain types of cardiovascular disease) and conditions that solely or disproportionately affect women.

2.4 Determine how to best define the appropriate representation of women in a given study:[40]

- Develop and evaluate metrics to measure the level of representation of demographic subgroups in clinical studies, which may ultimately support FDA-regulated product approvals and marketing authorizations.
- Evaluate to what extent the definition of the appropriate representation will affect the ability to identify sex differences (i.e., does your metric result in a sufficient number of women being included to reveal possible sex differences?).

2.5 Develop approaches and tools to track the inclusion of women in clinical studies, their demographic profiles, and the extent of subgroup analysis.

PRIORITY AREA 3: ADVANCE BIOMARKER SCIENCE

Develop tools and methods that can help identify, evaluate, and qualify predictive or prognostic clinical and nonclinical biomarkers and surrogate endpoints.

A biomarker is a characteristic (such as a physiologic, pathologic, or anatomic characteristic or measurement) that is objectively measured and evaluated as an indicator of normal biological processes, pathologic processes, or biological responses to therapeutic intervention.[41] More research is needed to identify biomarkers for assessing medical product safety and effectiveness in women throughout a product's life cycle, including to facilitate predictions in preclinical development that can be used during product development as well as to monitor safety and effectiveness after marketing (e.g., during post-approval testing and surveillance). Further, research in this area is needed to identify biomarkers that may aid our ability to detect, diagnose, and predict conditions that predominately affect women.

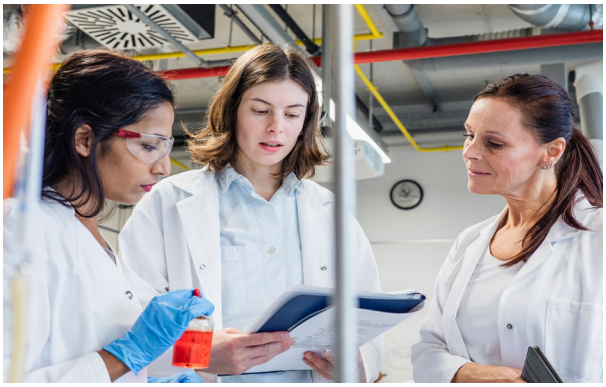
clinical practice, rather than as trials or studies performed under strictly controlled conditions.

[40] Consolidated Appropriations Act, 2023, Pub. L. No. 117-328, 136 Stat. 4457 (2022), https://www.congress.gov/117/plaws/publ328/PLAW-117publ328.pdf. The Food and Drug Omnibus Reform Act of 2022 (FDORA) requires sponsors to provide a diversity action plan.

[41] Section 507(e)(1)(A) of the FD&C Act (21 U.S.C. 357(e)(1)(A)); Section 507(e)(1)(B) of the FD&C Act (21 U.S.C. 357(e)(1)(B)); Biomarkers Definitions Working Group, "Biomarkers and Surrogate Endpoints: Preferred Definitions and Conceptual Framework," *Clinical Pharmacology & Therapeutics* 69, no. 3 (March 2001): 89-95, https://doi.org/10.1067/mcp.2001.113989; "About Biomarkers and Qualification," Biomarker Qualification Program, FDA, HHS, content current as of July 7, 2021, https://www.fda.gov/drugs/biomarker-qualification-program/about-biomarkers-and-qualification#BEST_Glossary. The definition of "biomarker" includes surrogate endpoints.

Certain biomarkers may be eligible for use as surrogate endpoints.[42] For purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure, that is thought to predict clinical benefit, but is not itself a measure of clinical benefit.[43] Depending on the strength of the evidence supporting the ability of a marker to predict clinical benefit, the marker may be a surrogate endpoint that is known to predict clinical benefit (a validated surrogate endpoint that could be used for traditional approval); a surrogate endpoint that is reasonably likely to predict a drug's intended clinical benefit (and that could therefore be used as a basis for accelerated approval); or a marker for which there is insufficient evidence to support reliance on the marker as either kind of surrogate endpoint (and that therefore cannot be used to support traditional or accelerated approval of a marketing application).[44]

Biomarkers can be used to help ensure that safety concerns specific to women can be identified early in medical product development and to help women enrolled in clinical studies avoid ineffective or unsafe treatments. Additionally, biomarkers may be able to identify differences in response to an FDA-regulated product resulting from other factors, like age, sex, and race or ethnicity.



Public health in general will benefit from research in this area. For example, biomarkers could be used to identify sex differences in responses to medical products, improving the availability of safe and effective medical products for all Americans. More specific biomarkers could also help improve the efficiency of clinical studies and accelerate the development of beneficial medical products.

Research in this area should aim to:

- Identify, develop, evaluate, and qualify biomarkers that can better measure and predict the safety and effectiveness of FDA-regulated products in women in non- or preclinical and clinical studies.
- Expand the FDA's knowledge of diagnostic, prognostic, and predictive biomarkers that can detect and predict the severity and progression for conditions in women and identify patients at risk for adverse events.

[42] "Surrogate Endpoint Resources for Drug and Biologic Development," Development & Approval Process | Drugs, FDA, HHS, content current as of July 24, 2018, https://www.fda.gov/drugs/development-resources/surrogate-endpoint-resources-drug-and-biologic-development.

[43] CDER, FDA, HHS, "Expedited Programs for Serious Conditions | Drugs and Biologics (Final)," (Silver Spring: FDA, 2014), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics.

[44] FDA, "Expedited Programs for Serious Conditions."

Important considerations in biomarker development include, for example, pre-analytical considerations such as sample collection, storage, and transport to ensure analyte/sample stability; the use of analytically validated (i.e., with sensitivity, specificity, accuracy, reproducibility) assays to ensure reliable biomarker data; reproducibility using a learn and confirm paradigm (i.e., use of datasets to test and confirm); and studies showing that the biomarker reliably reflects the clinical concept of interest.[45]

Objectives

3.1 Identify, develop, and evaluate biomarkers to be used in the assessment of products related to conditions that solely affect women.

- Assess the sensitivity, specificity, accuracy, reproducibility of biomarkers.
- Document the evidence supporting the correlation of identified biomarkers as diagnostic tools, indicators of health or disease processes, or in therapeutic response. For example, conditions such as endometriosis, polycystic ovary syndrome (PCOS), and uterine fibroids could benefit from an understanding of biomarker sensitivity and specificity.

3.2 Identify, develop, and evaluate biomarkers for the identification of sex differences in the performance of medical products.

- Assess the sensitivity, specificity, accuracy, reproducibility of biomarkers.
- Document the evidence supporting sex differences in the correlation of identified biomarkers as indicators of health or disease processes, or in therapeutic response.

3.3 Identify, develop, and evaluate biomarkers used to characterize the likelihood, presence, or status of a disease or condition, or to identify groups of women who are more likely than others to experience an unfavorable effect from a medical product.

- Assess the expected performance and clinical performance of biomarkers.
- Document the evidence supporting identified biomarkers as indicators of health or disease processes, or in therapeutic response.

[45] FDA, "Surrogate Endpoint Resources." For biomarker qualification, additional considerations include context of use (COU) of the biomarker in drug development; biological rationale for use of the biomarker; and characterization of the relationships among the biomarker, the clinical outcomes, and the treatment (where applicable) required for the proposed COU.

PRIORITY AREA 4: EXPAND DATA SOURCES AND ANALYSES

Identify, develop, and evaluate data sources and efficient techniques for data mining, data linkage, and large data set analysis that can be used to assess the post-market safety and effectiveness of FDA-regulated products.

Clinical studies for product approval or marketing authorization are usually conducted in controlled settings. As a result, they may not uncover or predict all adverse events that can occur during broader clinical use. Some safety issues are revealed only after a product is marketed and used in a larger, more diverse population under real world conditions. In addition, the 21st Century Cures Act,[46] enacted in 2016, requires that the FDA evaluate the potential use of real-world evidence (RWE) to help support approval of new products or new indications for existing drugs or to satisfy post-approval study requirements.

Real world data (RWD) include data derived from electronic health records (EHRs), claims and billing data, data from product and disease registries, patient-generated data including in home-use settings, and data gathered from other sources that can inform on health status. RWE can be generated using RWD through various study designs or analyses, including but not limited to, randomized trials,[47] externally controlled trials, and observational cohort studies.[48]

Proposed research in this priority area can explore improving safety signal[49] detection, data collection capabilities, and data standardization and harmonization to enable the use of RWD to evaluate the safety and effectiveness of FDA-regulated products. Identifying and using various RWD sources is especially critical for gathering evidence for diverse populations of women, including pregnant or post-menopausal women using regulated products.

[46] 21st Century Cures Act, Pub. L. No. 114-255, 130 Stat. 1033 (2016), https://www.congress.gov/114/plaws/publ255/PLAW-114publ255.pdf; "21st Century Cures Act," Laws Enforced by FDA, FDA, HHS, content current as of January 21, 2020, https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/21st-century-cures-act.

[47] "Project Pragmatica Advancing Evidence Generation for Approved Oncology Medical Products," Oncology Center of Excellence, FDA, HHS, content current as of February 8, 2024, https://www.fda.gov/about-fda/oncology-center-excellence/project-pragmatica

[48] FDA, HHS, Framework for FDA's Real-World Evidence Program (Silver Spring, FDA, 2018), https://www.fda.gov/media/120060/download.

[49] CDER and CBER, FDA, HHS, "Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment: Guidance for Industry (Final)," (Silver Spring: FDA, 2005), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/good-pharmacovigilance-practices-and-pharmacoepidemiologic-assessment. For purposes of this roadmap, the phrase safety signal refers to a concern about an excess of adverse events compared to what would be expected to be associated with a product's use. Safety signals can arise from post-market data, preclinical data, and events associated with other products in the same pharmacologic class.

Research in this area should aim to:

- Provide the FDA with the tools needed to integrate and interpret diverse data to support evaluation of safety and effectiveness of FDA-regulated products used by women.
- Provide additional tools to help identify adverse events in women and support changes in shared decision-making between health care providers and patients.

The potential public health benefits of advancements in evaluating the safety and effectiveness of FDA-regulated products in the post-market setting are substantial. The FDA is committed not only to supporting research that facilitates the pre-market review of medical products, but also to funding research on marketed products to assist in assessing whether these products are promoting and protecting public health for diverse populations of women who are using them.

Objectives

4.1 Evaluate U.S. and international RWD sources for use in the identification of the potential adverse effects and sex differences on the safety and effectiveness of FDA-regulated products used by women. Example sources may include:

- Registries
- EHRs
- Administrative claims databases (including, but not limited to, Medicare and Medicaid data)
- Surveillance databases
- Adverse event reports

4.2 Evaluate methodologies for the identification of clinically relevant sex and gender differences, using a variety of RWD sources.

4.3 Conduct studies using RWD sources to evaluate the safety and effectiveness of FDA-regulated products used by women, including the examination of sex and gender differences.

4.4 Develop efficient data mining and analysis techniques that can be used on data sets that can specifically identify women's health predictors, outcomes, and risk factors on a larger scale.

4.5 Develop and evaluate data standards related to sex and gender constructs in RWD, such as but not limited to EHRs and administrative claims data.

PRIORITY AREA 5: IMPROVE HEALTH COMMUNICATIONS

Develop, evaluate, increase, and facilitate the awareness and use of tools and methods to foster the creation of easily accessible, clear, and useful information about FDA-regulated products used by women to help women and health care professionals make informed health-related decisions.

Consistent with one of the FDA's strategic priorities,[50] the FDA seeks to provide consumers and health care professionals with the information they need to make informed decisions about the use of FDA-regulated products. Research in this area should identify and evaluate methods for communicating information about FDA-regulated products, including truthful and non-misleading risk and benefit information to diverse populations of women. Research should examine individual and situational factors that may influence the access to, understanding of, and use of such information. Additionally, specific strategies should be explored for communicating risk–benefit information to any women who may find product use or risk information unclear (e.g., for limited English proficient speakers). Health information for consumers should be easily accessible and tailored to the intended audience.

With a better understanding of how to create communication strategies to reach specific populations of women more effectively, the FDA can provide patients, caregivers, consumers, and health care professionals clear and useful health-related information.

Research in this area should aim to:

- Identify approaches to create, disseminate, and maximize the use of effective health communication materials for diverse populations of women.
- Promote access to truthful and non-misleading information about the benefit and risk of FDA-regulated products and tailor the information to women's needs.
- Support product labeling and other FDA communications for health care professionals who will benefit from clear and readily available prescribing, dispensing, product use, and safety information.

Objectives

5.1 Examine how factors related to an individual (e.g., sex, gender, age, literacy level, first language) can affect a woman's access to and understanding of FDA-regulated product information and its influence on subsequent health-related decisions.

[50] FDA, *Advancing Regulatory Science* (2011), See strategic priority # 8: Strengthen Social and Behavioral Science to Help Consumers and Professionals Make Informed Decisions about Regulated Products.

5.2 Identify new methodologies that aim to promote the development of easily understandable health communication materials for diverse populations of women.

5.3 Develop new and improved approaches to disseminate FDA health information for women, including assessing the awareness and accessibility of these communications.

5.4 Evaluate the reach and impact on desired outcomes (i.e., effectiveness) of FDA communications about FDA-regulated products used by women, including but not limited to identifying and evaluating methods for communicating:

- FDA information to specific populations of women, including older women, women with disabilities, caregivers, pregnant women, and women with limited English proficiency or lower literacy levels.
- Information about sex and gender differences.
- Risks of certain medical product exposures (including products given to pets or animals), food consumption (e.g., seafood), and the use of tobacco and non-tobacco nicotine products on genotoxicity, cancer, reproduction, pregnancy, and lactation.
- Information about drug exposure while pregnant or breastfeeding.
- Information for healthcare professionals, consumers, and researchers about women's participation in clinical research.
- Culturally sensitive information, which is especially important when engaging with diverse patient populations, and the disparities in the health status of people from different racial, ethnic, socioeconomic, religious, and cultural backgrounds.

5.5 Examine the effectiveness of the various channels by which the FDA communicates health information for women. Leverage this information to improve future FDA health communications for women.

5.6 Explore methods for using social media and other communication channels to identify gaps in knowledge, misinformation, or patient and provider perspectives about specific women's health topics and related FDA-regulated products. Identify and evaluate possible challenges related to how social media and other communications channels are being used by others to inform and influence women about FDA-regulated products.

PRIORITY AREA 6: PROMOTE EMERGING TECHNOLOGIES AND METHODOLOGIES

Support the identification of sex differences related to the use of emerging technologies and methodologies, and explore strategies to leverage emerging technologies to address women's health conditions.

Science and medical care continue to evolve, and new medical and scientific technologies continue to emerge. Some of these emerging technologies include nanotechnology, pharmacogenomics, novel imaging technologies and methods, 3-D printing, digital twins, and developments in regenerative medicine.

Research in this area should aim to:

- Develop and adopt new methods, tools, and approaches for evaluating new technologies that consider sex and gender differences.
- Enhance the FDA's ability to evaluate innovative products and novel technologies to efficiently integrate beneficial new products into mainstream health care for women.
- Enrich the FDA's knowledge and application of emerging technologies, methodologies, and tools to address women's health concerns, specifically in understudied areas.
- Advance the understanding of the possible effects of sex differences on the use of these new technologies and scientific fields.
- Create predictive models that take sex, disease status, and comorbidities, and other critical factors into consideration.

This research will enhance understanding of the impact of novel technologies on women's health and will have the potential to change the landscape of medicine and benefit women's health care. Additionally, the consideration of sex differences during the development of new technologies will facilitate advances in precision therapy.

Objectives

6.1 Examine sex differences early in the development of innovative health products, new materials, and novel assessment tools and methodologies, including but not limited to:

- Nanotechnology
- Precision medicine
- Pharmacogenomics (metabolomics, epigenetics)
- Novel imaging technologies and methods for improved diagnosis
- 3-D printing
- Digital twins
- Digital health technologies
- Artificial intelligence, including machine learning
- Stem cells and regenerative medicine
- Next-generation sequencing[51]

6.2 Utilize and adopt novel and innovative tools and methodologies to help address gaps in understanding sex differences and addressing women's health concerns.

6.3 Develop new and leverage existing tools and novel animal, *in vitro*, and computational (*in silico*) models, including those for use in clinical studies of the safety and effectiveness of FDA-regulated products used by women and to study sex differences. Examples include, but are not limited to:

- Developing *in vivo, in vitro* (including but not limited to organoids), and computational (*in silico* or digital twin) models to evaluate regulated product safety and effectiveness during pregnancy.
- Developing innovative disease models for conditions that affect women, including for rare diseases.
- Developing models that incorporate human genetics, genomics, molecular signatures, and biomarkers for diseases influenced by sex.

[51] FDA, HHS "FDA Finalizes Guidances to Accelerate the Development of Reliable, Beneficial Next Generation Sequencing-based Tests," news release, April 12, 2018, https://www.fda.gov/news-events/press-announcements/fda-finalizes-guidances-accelerate-development-reliable-beneficial-next-generation-sequencing-based.

- Determining factors relevant to therapy selection and medication dosing considerations in women.
- Evaluating dietary supplements for sex differences in safety.
- Identifying unique risks to women associated with the use of regulated products, particularly products predominantly used by women.
- Further evaluate the factors of concern for women users to explore any sex- and gender-associated risks.
- Identifying categories of products that could be expected to have risk profiles that differ for women versus men; develop a framework for capturing and evaluating the safety and effectiveness of the products in these categories. For example, one unique consideration is contact exposure through use of topical products, such as transdermal estrogen (used for birth control or symptoms of menopause) that may result in inadvertent product transfer to others. Because women are more likely than men to be caregivers, such differential factors should be explicitly identified and evaluated for specific products.

PRIORITY AREA 7: COMBAT EMERGING HEALTH THREATS

Develop and improve strategies and capabilities to better prepare for, monitor, and respond to emerging threats to women's health.[52]

Climate-related weather events, changing ecosystems, changes in global trade, social change, and evolving understanding of novel technologies can lead to emergence of novel threats. There is an increasing understanding that the health of humans, animals, and the environment is intertwined, and One Health approaches are necessary to address emerging threats that develop in any one of these areas with effects on the others.[53]

Proposed research in this priority area should explore strategies to better prepare for and mitigate emerging threats to women's health. In this context, an emerging threat may: be a new, recently discovered, and/or increasingly prevalent concern; be potentially associated with an increased risk to the health of women; and either originate from an FDA-regulated product or be mitigated by an FDA-regulated product.

[52] The FDA recognizes that sex and gender are distinct concepts and may not be concordant.

[53] "One Health: It's for All of Us," Animal Health Literacy, FDA, HHS, content current as of July 15, 2023, https://www.fda.gov/animal-veterinary/animal-health-literacy/one-health-its-all-us. The strategies include research with One Health focused on emerging health threats such as environmental, zoonotic, plant, and human components.

Research in this area should aim to develop, assess, and improve strategies and methodologies that:

- Develop tools to identify public health threats, prevent them from becoming crises, and promote public health security, with a focus on women.
- Ensure that medical countermeasures—such as drugs, vaccines, and diagnostic tests—include women during development and include an evaluation of sex differences.

Objectives:

7.1 Improve capabilities and strategies for monitoring the safety and effectiveness of FDA-regulated products used by women, such as by supporting targeted, ongoing real-world investigations. For example, more research is needed to better understand:

- The biocompatibility of materials related to medical devices implanted in women.
- The effects of inks and colors (absorbed through activities such as tattooing or microblading) on diverse populations of women.
- Sex differences in the adverse effects related to use of electronic nicotine delivery systems (for example, e-cigarettes).[54]

7.2 Develop plans and protocols to manage and respond to emergencies involving or affecting regulated products which may pose a threat to women's health. Emergency preparedness and response plans should include studies of sex and gender differences to better understand the needs of women (including the impact on pregnant and lactating women). In addition, diagnostic tools, vaccines, medical countermeasures, and other therapies should be studied in both women and men.

7.3 Explore the use of FDA-regulated therapeutic products to counter an existing threat to women's health that is growing—or has grown—into a crisis, including maternal mortality and morbidity, congenital syphilis, mental health disorders, and other emerging threats.

[54] "Research," Tobacco Science and Research, Center for Tobacco Products (CTP), FDA, HHS, content current as of July 29, 2019, https://www.fda.gov/tobacco-products/tobacco-science-research/research.The extent of OWH funding of initiatives related to tobacco products is limited, to some extent, by authorities laid out in statutory language authorizing the Center for Tobacco Products (CTP). CTP funds research related to its statutory authority.

The Road Ahead

OWH works to protect and advance the health of women by collaborating with FDA's centers and offices, academia, government agencies, women's health organizations, and other stakeholders. These efforts spur innovation in scientific knowledge, resulting in the discovery of novel methodologies, technologies, and improvements in the diagnoses and treatment of health conditions and diseases that impact women. "The Women's Health Research Roadmap" provides a science-based framework to support and fund future research activities that:

- Advance the evaluation of sex and gender differences in the safety and effectiveness of FDA-regulated products.
- Investigate health conditions and diseases solely or disproportionately affecting women.
- Promote the participation of women in clinical research.

The roadmap outlines priority areas in which new or further research is needed. In applying this updated roadmap, OWH seeks to fund research that will expand our understanding of the science of women's health, close knowledge gaps, and contribute to policy, outreach, and education initiatives important for the health of women.

OWH's Research Program utilizes the Roadmap to further the FDA's public health and consumer protection mission and the efficient use of FDA resources. This roadmap helps reinforce the agency's ability to effectively address women's health research questions and build women's health science into cross-agency research activities. Research addressing these seven priority areas are directly relevant to the FDA as it

makes regulatory decisions related to the safety, effectiveness, and security of FDA-regulated products used by women. With this roadmap, OWH will continue to fund FDA research using a priority-focused approach to address the complex and evolving regulatory questions, opportunities, and challenges related to women's health.

When selecting projects for funding, OWH will consider questions, including but not limited to:

- Does the research address a priority area outlined in the roadmap?
- Is the research aligned with the FDA's regulatory science priorities or other strategic goals?
- Does the research address a regulatory question with the potential for regulatory impact, policy change, or revised guidance?
- Does the research address a knowledge gap in relation to public health needs of women or where women have few therapeutic options?

This roadmap will be used by OWH as a tool to promote women's health research, advance strategic and diverse research investments, maximize research impact, and improve collaboration within and between key stakeholder groups.

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