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Critical path

# Advancing women's health via FDA Critical Path Initiative

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**Studying sex and gender differences is critical to understanding diseases that affect women solely, disproportionately or differently from men. Although inclusion of both sexes is essential in clinical research, advanced technology and analysis methods offer tools to define complex biological and physicochemical differences and improve prevention, diagnosis and treatments for diseases in women and men. This paper identifies the potential for biomarker development, pharmacogenetics and bioinformatics in research under the FDA Critical Path Initiative.**

## Introduction

Sex is presently recognized as an important biological variable. FDA and NIH policies have sensitized researchers to the importance of sex differences stimulating a gradual increase of women enrollment in clinical studies over the last decade. There is now substantial evidence of sex differences in disease prevalence, disease presentation and response to treatment. It is obvious from these findings that simply including women to fulfill regulatory standards will not suffice for causal identification of response differences. With the emergence of personalized medicine, a mechanistic understanding of sex differences that incorporates cutting edge research and evaluation tools such as genomics, biomarkers and bioinformatics is fundamental to progress in medicine. This paper focuses on sex as one essential variable in understanding

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differences in response to therapies. It should be noted that other variables (e.g. age, race) contribute to variability in response, making the evaluation of therapies a complicated process.

## Key technologies

*Exclusion of women from clinical trials: basis and path forward*

Despite a lack of compelling reasons to exclude women from research studies, continued concern exists on the part of investigators about the inclusion of women in clinical trials. Excluding women, particularly those of child-bearing age, stems from fear of medical liability should a trial participant become pregnant while receiving treatment. Additionally, it is postulated that hormonal fluctuations of the ovarian cycle would amplify sample heterogeneity requiring a larger sample size to detect statistical differences. By and large, females have been generally considered harder to study [1]. However, exclusion of women from biomedical research and clinical trials have caused an unintentional consequence of increased harm to women in the day-to-day practice of medicine because disease prevention, diagnosis and treatment paradigms are derived from clinical studies conducted primarily in men and inappropriately extrapolated to women. Scientific, social and political forces in the last decade have resulted in changes in regulatory policies regarding the inclusion of women in clinical studies and

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analysis of results by sex [2,3]. Since sex differences are pervasive across all of biological systems and at all levels of biological organization, the Institute of Medicine concluded that the study of sex differences must be conducted at multiple levels – gene, cell, tissue, organ and organism – and that sex differences be studied at every stage of life, from conception through death [4]. Studying sex (biological, genetic, phenotypic) and gender (behavioral, social) effects as separate entities is also meaningful in determining diagnosis and treatment options [5]. There is mounting evidence of sex-based differences in disease presentation and treatment response. This reaffirms that women as a subpopulation need to be included and evaluated prospectively and, more importantly, mechanistically, through all phases of medical product development.

The female phenotype is surely not the sole source of variability in clinical assessment. Non-homogeneity of study populations as a whole is derived from other underlying biological and environmental factors. This knowledge has rendered a new dimension to understanding variability in clinical symptoms and response to treatment to optimize medical care.

#### *The Critical Path Initiative: a haven for subpopulation analysis*

Traditionally, clinical trials are designed to compare treatments, or to compare treatment with nontreatment (control) in representative populations. This approach of measuring efficacy through population means fails to address safety or efficacy issues at the subpopulation or individual patient level. Frequently subpopulation analyses provide only exploratory findings and often remain unreported in FDA reviews, product labeling or publications.

Adequate assessment of sex differences in response can be undertaken through subpopulation analysis only if sufficient numbers of both sexes are enrolled in clinical studies, which can be costly and time consuming. Innovative approaches to study design and statistical methodologies utilizing novel technological tools offer an alternative to simply increasing the size of study populations. Owing to growing concern of rising product development costs, coupled with declining medical products reaching the marketplace, FDA launched the Critical Path Initiative (CPI) in 2004, a call-to-action for the use of modern research and analysis methods as well as innovative tools to facilitate drug, biologic and device development [<http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html>] [6]. These tools include genetic, genomic or proteomic markers, advanced medical imaging, use of biomarkers to predict risk of side effects and response to treatment and alternative clinical trial designs and data analyses methods. The CPI provides a framework for the scientific understanding of response variation by subpopulations, genetics and other factors such as demographics.

FDA's Office of Women's Health (FDA-OWH) protects and advances the health of women through policy, science and outreach and advocates for inclusion of women in clinical trials and analysis of sex/gender. This is an opportune time for FDA-OWH to further women's health under the auspices of the CPI to explore the causal underpinnings of male–female differences.

#### *Women's health on the critical path*

The multidisciplinary goals of CPI are a daunting task for a single institution or agency and require scientific collaborations to leverage resources through partnerships. In this context, FDA-OWH partnered with the Society for Women's Health Research [<http://www.womenshealthresearch.org/>] to convene a thought leaders' workshop. One of the goals of this workshop was to discuss the role of CPI of FDA in furthering the understanding of sex/gender differences to improve women's health. The workshop addressed the importance of understanding the biological differences between men and women in the context of developing tools to improve and accelerate the development of medical products. The development of sex-specific biomarkers, applications of pharmacogenomics to explore sex differences, and the need for data standardization to make cross-organization repositories accessible and usable were considered important areas for further research [7].

#### *Promising technologies*

##### **Biomarkers**

Product development using conventional methods of hypothesis testing, trial design and data analysis is costly and time consuming. It is currently reported that only about 10% of investigational drugs make it to the market [7,8]. Utilizing measurable characteristics (e.g. biomarkers) that reflect physiological, pharmacological or disease processes in animals or humans in early decision making should increase the probability of success. Biomarkers may be derived from methods such as imaging, serum or genetic assays, or physiological tests and could provide outcome predictions. Using biomarkers for diagnosis, evidence of efficacy and evaluation of toxicity, or as surrogates for clinical endpoints are not novel concepts in product development. Biomarkers are currently used to determine early attrition, define disease and its progression, identify target populations, select doses, enrich clinical trial populations, monitor risk and benefit, predict clinical trial outcomes and define primary end points. Because biomarkers may fulfill a range of applications in product development, the evidentiary standard to which each one is held varies by its role. For instance, a biomarker used by pharmaceutical companies for internal decisions may not meet the qualification standards needed by FDA for its intended use and one that substitutes as a surrogate endpoint may not actually be predictive of the clinical

endpoint. These 'research grade' markers and potential endpoints, therefore, may not contribute to the regulatory evaluation process.

Stable biomarkers help identify subjects who are likely to respond to a treatment intervention and can be used to enrich the clinical trial population to reduce cost. Such predictive patient biomarkers also serve as tools to optimize therapy when few alternatives exist or when consequences of therapeutic failures are formidable. Tamoxifen, used for breast cancer, illustrates the utilization of biomarkers to select patients most likely to respond favorably. Tamoxifen has demonstrated better response for women whose tumors were estrogen receptor positive [9].

Unlike stable biomarkers, dynamic biomarkers must be assessed repeatedly during treatment. Change from baseline in blood levels of analytes (e.g. protein or metabolite) or in the level of gene expression may provide an efficacy or safety response signal. Imaging biomarkers also provide diagnostic as well as real-time dynamic changes to disease. Functional magnetic resonance imaging (MRI) in men and women have revealed that a significant number of women rely on both hemispheres of the brain for language whereas men predominantly rely on the left hemisphere. An understanding of such diagnostic differences suggests that many women suffering a left-sided stroke may be protected from decrements in their language performance [10].

Surrogate endpoints that substitute for disease outcome require appropriate qualification and a high evidentiary standard to substitute for a clinical endpoint. Surrogate endpoints currently in use include HIV viral load as a surrogate for response to HIV treatment, and low-density cholesterol levels as a surrogate for response to treatments to prevent coronary artery disease.

Biologic similarity for disease staging and response between men and women is often taken for granted without prospective efforts to reveal or understand differences. For instance, an observed response different from that documented in a clinical trial may be dismissed as 'atypical' without further exploration of its origin. A sex-based understanding of how the biomarker relates to the disease staging and progression as well as its alteration in response to treatment is crucial for optimizing treatment in men and women. An assessment of the interaction between sex and age and ethnicity is likely as important. Some have recommended that newly available technological advances (e.g. genomic, proteomic microarrays, gas chromatography, tandem mass spectroscopy, high performance liquid chromatography) allow for evaluating sex differences at all stages of disease progression and medical product development [7]. Imaging modalities and diagnostic tests also need evaluation for potential sex related outcome variations. A centralized repository of annotated markers by sex including cells, tissues, imaging, electrocardiograms, among others would be beneficial for the understanding of

underlying differences. More research towards the development of clinically qualified biomarkers for sex-specific clinical outcomes is needed to expand the current list [[http://www.fda.gov/cder/genomics/genomic\\_biomarkers\\_table.htm](http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm)].

#### Pharmacogenomics

Genes on the sex chromosomes can be expressed differently between males and females, causing biological heterogeneity seen down at the cellular level. Gene expression profiles on somatic tissues (e.g. liver, muscle, brain and adipose) also demonstrate sexual dimorphism [11]. The ability to characterize the contributions of genetic polymorphisms to disease prevalence and response to therapy is a rapidly evolving field. Mechanistic differences seen in biochemical or physiological processes between patient subpopulations are being investigated at the genomic level. Future applications of genomic technologies will serve to detect disease susceptibilities, aid drug discovery and tailor treatments to individual patient characteristics. These differences may manifest as anecdotal research findings that, when studied further, may reveal the underlying mechanistic pharmacogenomic basis. For instance, pharmacokinetic differences have previously been reported between men and women (e.g. erythromycin, verapamil, fluvoxamine, olanzapine) which may be owing to differences, at least in part, in gene expression coding the metabolizing enzymes [12–14]. Women are more likely to be affected by immune-mediated inflammatory diseases such as lupus erythematosus and rheumatoid arthritis [15], alosetron has shown efficacy primarily in women with irritable bowel syndrome [16], baseline plasma concentrations of HIV RNA are lower for women, and men tolerate didanosine better than women [17]. Women have longer heart rate corrected QT intervals than men and are more susceptible to develop torsades de pointes after administration of drugs that prolong cardiac repolarization, for example antiarrhythmics, terfenadine and erythromycin [18–20]. Female sex has been identified as one of the risk factors for life threatening cardiac events among Long QT Syndrome mutation confirmed patients [21]. Although many such examples appear in the literature, several go unreported. Exposure differences (e.g. differences in plasma concentrations, maximum plasma concentrations, area under the plasma concentration versus time curve) may partly explain the overall response differences between men and women; the lingering question exists regarding the genomic basis for disease prevalence and treatment response.

Continued understanding and reporting of genetic polymorphisms, such as single nucleotide polymorphisms, as markers with subpopulation dependent outcomes will further revolutionize the pharmacogenomic advances in health science and expedite the underpinnings of personalized medicine.

## Bioinformatics

The National Institutes of Health through the work of the Office of Research on Women's Health (ORWH) prospectively ensures that studies funded through its institutes include a representative number of women in clinical trials [[http://orwh.od.nih.gov/pubs/SMR\\_Final.pdf](http://orwh.od.nih.gov/pubs/SMR_Final.pdf)]. FDA, on the contrary, provides guidance to sponsors on safety and efficacy evaluations by subpopulation for drugs, biologics and devices development. New Drug Applications (NDAs) and Investigational New Drugs (INDs) submitted to the FDA are required by regulations to include information on trial participation, safety and effectiveness for important demographic groups such as sex, age and racial subpopulations ([21] CFR 314.50 and 21 CFR 312.33). Currently, however, there are no widely established data standards or automated analyses tools for electronic data entry, retrieval and analysis systems that could be used across numerous applications submitted to the FDA. This limits ability of FDA to systematically track and assure adequate representation of patient subpopulations (e.g. women) in clinical studies. Additionally, this data resides with multiple academic, industry and regulatory research bodies for which data standards and securely maintained data repository systems are needed to enable assimilation and analyses by sex and other subpopulations within and across studies. Applications of information technology infrastructure to the life sciences databases, that is bioinformatics, hold tremendous promise to this end. Under the CPI, FDA is actively participating in multidisciplinary consortia and other partnerships intended to create data standards to enable pooling and analyzing with concurrent security of proprietary information. Through CPI, FDA is revamping its IT environment and infrastructure.

Clinical Data Interchange Standards Consortium (CDISC) is a not-for-profit organization that develops clinical data standards for use across industry and regulatory agencies. CDISC supports the development of global, platform-independent data standards that enable information system interoperability to improve medical research and regulatory review of therapeutic products [22]. FDA is working with this consortium to revamp its pre-clinical and clinical data standards and requisite FDA infrastructure to facilitate the use of data complying with standards. Steps initiated to achieve this goal include facilitating information exchange, creating central standardized data repository, enabling secure electronic data submission and providing common analysis tools and secure access to data. NDAs are now being compiled using a standardized data format for submission to the FDA. A preliminary assessment by FDA-OWH of the few NDA applications submitted in this standardized format demonstrated the feasibility of tracking patient participation and other information by subpopulations in clinical trials [<http://www.cdisc.org/publications/interchange2006/session8/EllenPinnowCDISC2006Pinnow.pdf>] [23].

Structured product labeling (SPL) allows labeling information for FDA regulated products to be publicly available in machine-readable formats enabling rapid searches and sorting. Adverse events or other relevant information for women and men could be easily searched using this mechanism.

Some other important applications of bioinformatics include standardized annotations for specimen repositories including genes and proteins, issues of property rights and proprietary data, terminology for demographic descriptions, symptoms, outcomes and case report forms. Communication of health care information in a standardized manner will be revolutionized through bioinformatics advances.

## Final remarks

The rising cost of medical product development and the increased rate of attrition are impediments to health care product development. It is crucial to explore and adopt more efficient ways to evaluate safety and efficacy of medical products. Despite large investments in clinical trials, several questions related to varied responses in subpopulations remain unanswered. Although inclusion of adequate numbers of women and men, as well as other demographic groups, allows for a better understanding of subpopulation differences, it concurrently drives up the cost of and time for product development. Pharmacogenomic and biomarker guided drug, device and biologic development have paved a new path towards personalized medicine using mechanistic rather than empirical approaches.

FDA-OWH in concert with the collaborating scientists in FDA is proactively undertaking research to foster a better understanding of sex differences by utilizing biomarker and pharmacogenomic technologies. Some ongoing studies include exploring molecular mechanisms for adverse events of anti-retroviral agents, toxicity profiles for chemotherapeutic agents, and the genetic basis for differences in response to lupus therapy. Biological and imaging biomarkers for cardiovascular diseases and cancer survival are being explored. FDA-OWH is collaborating on bioinformatics projects for the development of data exchange and regulatory submissions standards as well as enabling SPLs to be machine readable through XML tagging. Through partnerships with academic and other government organizations, exposure and response for drugs in understudied populations (i.e. pregnant women) are under way. Collaboration and utilization of a multidisciplinary approach is critical to foster a better understanding of the biology that governs sex and gender differences.

Research to better understand sex differences are not necessarily best served by simply including an adequate number of both sexes in clinical studies. The discovery and utilization of novel technological tools to understand the mechanistic underpinnings of subpopulation differences holds immense promise to personalized medical care.

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