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# Sex Differences in FDA Regulated Products: Research for the Future

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The purpose of the workshop was to explore how sex influences disease and disease therapy regimens. It is known, for example, that women are disproportionately affected by several conditions in terms of incidence, diagnosis and response to treatment - women are more likely to contract rheumatoid arthritis, lupus, hepatitis, depression, irritable bowel syndrome and thyroid disease. The female response to treatment of many conditions is also different for women when compared to men. Thus, this Food and Drug Administration (FDA) workshop set out to identify critical gaps in FDA regulatory research, specifically addressing disparities in women's health; and to identify future research needs to address the impact of sex differences in FDA-regulated products.

Opening Remarks from Dr William Slikker, the Director of the FDA's NCTR center, were followed by that of Dr Ameeta Parekh, Director of Research, FDA Office of Women's Health, and the Associate Director of Regulatory Activities, Dr Margaret Miller; all of whom underlined the importance of an individual's sex in disease risk and drug therapy efficacy and safety. The opening speakers emphasised the need to understand how patient's sex impacts risk-benefit analyses for products regulated by the FDA.

Beverly Lyn-Cook (co-author of this report), PhD, the FDA NCTR Office of Women's Health co-ordinator and conference organiser presented on 'The state of women's health research'. Many diseases and therapies have now conclusively shown that sex bias exists. Dr Lyn-Cook showed that multiple hurdles must be overcome to elucidate why the bias in women's disease risk and treatment exists. These factors require investigations in basic biology and hormonal fluctuations, along with an understanding of cultural bias and an increase in clinical trials reporting of sex based statistics: the lack of these factors is currently preventing a complete understanding of the reasons for sex bias in susceptibility to many diseases and response to therapies. Dr Lyn-Cook finished with a call for more basic research to understand sex differences in disease and drug treatments in the interests of public health.

E. Fadiran, PhD, presented a talk entitled 'FDA data standardisation initiatives: implications for demographic analysis. The presenter outlined the need for standardisation of clinical trial analysis and standardised terminology. The current lack of standardisation means that cross-study comparisons are currently very difficult: for example, some studies label 'M' and 'F' for 'male' and 'female', whereas others might utilise '1'and '2'; or '1' and '0' to code for gender. However, there is some progress in this area with the development of new standardised clinical trial repositories, which will hopefully be utilised in the near future and will help in analysis of sex differences across all clinical trial data.

E. Treadwell, MD, presented 'Lupus: Where we are and where we need to go', Dr Treadwell commenced his lecture by outlining the difficulty of diagnosing this multifactorial disease -a disease that is female-prevalent (with 78% of patients being female). The presenter outlined the eleven separate criteria for lupus, the fact that many different organ systems may be affected (dependent on the individual); and he outlined the various antibody tests, which – alone - are often not enough to conclude a diagnosis of lupus: the physical symptoms in addition to the antibody tests may be used to give a diagnosis of lupus, but individual patients may not present with the same physical symptoms or antibody test results. Thus, there is a need to understand the disease of lupus at the molecular level in order to provide for better diagnostics.

The presenter then moved on to discuss the risk factors for lupus: patient sex being the most obvious major risk factor; also sulfa drug allergy, smoking, pesticide exposure, dark hair dyes, African American ancestry and early menopause are amongst a long list of those factors found to be correlated with increased risk. Genetic factors for increased risk include variations within the complement cascade; whereas at the inflammatory level, increased TNFalpha and other cytokines such as IL-6, IL-10, IL-18, IFN-gamma, Bcl2 and the Fas ligand have all been correlated with an increased risk of contracting lupus. Dr Treadwell moved on to the current therapies (constituting mainly a combination of immunosuppressants and steroids) and a need for improvement in the current accepted therapies, which have major side effects. The presenter outlined progress being made with more targeted therapies - such as with the antibody class of drugs. These potential antibody therapies include rituximab, LJP-394, and IVIgs from blood donors. Other promising approaches include plasmaphoresis and stem-cell transplants in combination with chemotherapy; along with DHEA supplementation (Although DHEA supplementation is only effective in those who are low in DHEA in the first place). Dr Treadwell finished by noting that better diagnostics and new efficacious therapies with less side-effect are required. Also, more research into the genetic targets and into how hormonal profile affects disease risk is of great importance.

Tiffany Powell, MD, presented a lecture entitled 'Body size misperception as a novel target in the obesity epidemic: insights from the Dallas heart study'. Dr Powell presented evidence describing that body size perception influences a variety of factors in relation to health behaviours, which may often result in adverse health outcomes. (For example, if an obese person does not perceive that they are obese, they are less likely to consult a doctor). Women are particularly at risk from body size misperception, as are those from certain cultural and/or socio-economic backgrounds (certain cultures or groups may perceive size to be more or less of an issue) - and

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thus at risk for these adverse health outcomes. Dr Powell stated that recognising and pinpointing these issues may help to prevent adverse outcomes in the future.

Ronda Henry-Tillman, MD, presented on 'Breast cancer: current therapies and the need for new potential targets'. Dr Henry-Tillman talked firstly about the fact that current predictive breast cancer risk models are not being adequately deployed and targeted to those most at risk; a problem, since the highest risk candidates need to be captured early in order to improve survival rates. Risk models take in to account genetic mutations with positive breast cancer correlation (such as within the *BRCA* gene), the incidence of first degree relatives who may have had breast cancer, and any radiation to the chest that may have occurred in the past. Since many high-risk candidates are not being targeted, they often fail to undergo mammography and diagnostic procedures. Recent improvements in diagnostic procedures outlined by the presenter include digital mammography (an improvement over the classical mammography procedure, particularly amongst younger women, though the higher sensitivity means a higher false positive rate); and needle biopsy of suspect lumps, which allows for same-day analysis. Recent improvements to treatments includes the use of 'reverse mapping': a procedure in which a dye is used during lumpectomy to illuminate lymph nodes, so nodes are not unnecessarily removed, thus preventing the sometimes debilitating side-effects of lymphedema following lumpectomy procedures. Masectomy reconstruction has also improved recently – surgeons now routinely save the outer skin of a patient (removing all the tissue underneath the skin) for a more uniform and easier reconstruction.

In terms of drug therapies, the targeting of triple negative (estrogen receptor, progesterone receptor,HER2/neu protein negative [ER/PR/HER]) breast cancer is proving particularly difficult to treat as there are no targeted therapies for this group of patients. Recent antibody therapies that have not proven as successful as hoped: these include anti-angiogenesis targeting antibodies such as bevacizumab, Her1 targeted therapies and vascular endothelial growth factor [VEGF] inhibitors. Dr Henry-Tillman described promising new therapies, such as the poly(ADP-ribose) polymerase [PARP] proteins (which are involved in DNA repair and programmed cell death) and EGF inhibitors, though more work is needed, particularly focusing on the high-need group of patients displaying triple negative breast cancer. The presenter concluded that more work is needed across all areas of breast cancer: from risk analysis, screening, diagnosis and treatment so improvements in mortality and quality of life (QoL) might be improved. Dr Henry Tillman also noted that tumour-targeting therapies specifically may help to improve these endpoints.

Sue-Chih Lee, PhD presented 'Physiologically-based Pharmacokinetic Modeling: Applications in Clinical Pharmacology and Women's Health'. Dr Lee presented a case for including factors that may predict for sex-based exposure in the clinic. Such models would factor in pharmacokinetic factors such as blood flow, CYP P450 enzyme expression and activity levels, drug-drug interactions, steady-state levels and predict for clinical exposure from *in-vivo* profiles. Future models for sex based dosage prediction that also incorporate pharmacodynamic factors are likely to be required in order to complement the pharmacokinetic factors.

Williams Salminen, PhD presented on 'Sex and hepatotoxicity'. Dr Salminen outlined rodent studies that show gender-specific hormone profiles, citing previous studies that show the growth hormone (GH) profile is the main influence in the rodent model of these gender-based divergences in liver enzyme expression. Dr. Salminen also examined the female preponderence for 'polypharmacy' (a trend among women to take more drugs and herbal /vitamin supplements simultaneously) and stated that a greater effort to record and be aware of polypharmacy may be helpful in monitoring the potential side-effects.

Tamara Nicolson, PhD (the author) presented on 'Sex differences in drug toxicity: the molecular bases'. Dr. Nicolson outlined the clinical data showing that for some drugs there are differences in drug efficacy and toxicity profiles between men and women. The presenter described two main mechanistic factors that are currently known to influence sex-based drug toxicity in humans: 1. Direct hormonal effects on drug targeting and drug metabolism pathways; and 2. the influence of the growth hormone (GH) axis (as outlined in the previous presentation). Since humans do not display 'male-only' or 'female-only' liver enzymes as the rodents do, differences in humans are likely to be more subtle, though the effects of a sexually-divergent GH profile may still be very significant in terms of drug toxicity. Unknown mechanisms may also play a role in addition to the two listed above (mechanisms such as 'X' chromosomal escape inactivation, which may result in females receiving 'double-dosage' effects): however, these areas remain extremely poorly studied, even in preclinical species, and so the potential effects are currently unknown. All of the potential mechanisms need to be studied in depth to gain an understanding of why men and women react differently to drugs.

Dr. Nicolson discussed the requirement for a preclinical predictive model for sex-based efficacy and toxicity and suggested the dog may be a preclinical species worth investigating for this purpose.

K. Barry Delclos, PhD presented 'Endocrine Disrupters: do environmental exposures to hormonally active agents pose a threat to human health?, outlining various mammalian in-vitro assays that have recently been developed to assess a naturally occurring and manmade compound's likelihood of endocrine disruption. Such assays include steroid receptor binding and activation, steroidogenesis and thyroid endpoint assays. However, it is unclear whether these assays are sensitive enough to pick up chronic, low-dose exposure endocrine disruption, and so efforts have been made to optimise *in-vivo* rat studies to predict for these, using genistein and bisphenol-A as model compounds. Results indicate that animals are adversely affected. However, it remains unknown how the human studies will correlate to the animal studies and more efforts are required to predict the translation to human. Furthermore, Dr Delclos outlined efforts at the molecular level that may be useful in predicting endocrine disruption (in a tissue-dependent manner). Endpoints still to be evaluated for this purpose include proliferation, apoptosis and cytokeratin 10; the monitoring of estrogen gene and estrogen-related expression levels; also monitoring of dysregulation of gene pathways shown to be involved with known endocrine disrupters (such as those pathways dysregulated upon Bisphenol-A exposure). Also in the future, DNA methylation patterns might be measured in various tissues to predict for endocrine disruption.

The final lecture of the workshop, 'Sex differences in clinical outcomes of anti-depressant medication' was presented by Sherry Ferguson, PhD. Dr Ferguson described how mental health issues constitute a very large economic and social cost (one that is currently rising), with depression specifically more prevalent in the female population. Dr. Ferguson outlined the current therapies for depression: Cognitive Behavioural Therapy (CBT), which has a success

rate of around 50%; where classical drug therapy with anti-depressants shows a success rate of around 54%, but typically only when taken on a long-term basis. Dr Ferguson described mechanisms of depression: serotonin and estrogen have both been shown in previous studies to have direct effects on depression, along with a link to other lesser-known mood effectors such as tryptophan hydroxylate. Of particular interest was the discussion surrounding the SERT (serotonin receptor) in an individual's development: previous studies showed that isoforms (there are two isoforms: 'long' and 'short') which influence susceptibility to depression and therapeutic efficacy. Dr. Ferguson described these previous studies: notably, the research showing that if patients have at least one 'long' allele of the SERT, it provides an effective predictor of whether an individual *female* will respond to SSRI therapy. Interestingly, this correlation was found not to be true for men. The mechanistic reasons for this are unknown, but thought likely to be due to hormonal influence. Furthermore, she described studies that show medical device therapies (such as repetitive transcranial stimulation) are not effective in women, but may have some limited efficacy in men.

Thus, risk for depression and also the efficacy of therapies is due to many factors: sex and SERT isoforms, along with environment, are strong predictors. Dr Ferguson summed up with a call to investigate new treatments for the 46% of those who do not respond effectively to current therapies.

## Conclusion

This was a varied workshop with clinical MDs and basic researchers participating in a cross-discipline interaction. Sex differences are becoming increasingly clear and obvious, and many of the speakers underlined the problems in disease diagnosis, treatment and assessment of variable risk factors. It is also clear that the potential for new therapies and dosage regimens based on a patient's sex might be considered in the future, though more understanding of mechanisms at the molecular level is required.

### Disclosures and supplementary information

*The views presented in this report do not necessarily reflect those of the US Food and Drug Administration or that of AstraZeneca.

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