

### The Impact of Sex and Gender on Medicines

Attention to sex and gender in biomedical, health and clinical research is an important quality and safety issue. Medicinal products are safer and more effective for everyone when clinical research includes diverse population groups. Historically, women's health issues have focused on reproductive health. Additionally there has been attention devoted to some gender issues, including how societal constructs—such as behaviour, socio-economic factors, culture, lifestyles—influence biological development and health.

Over the years, scientific knowledge has increasingly demonstrated that some treatments affect men and women differently. However, the proportion of treatments for which men and women respond differently is yet unknown. Many physiological and pathological functions are influenced by sex-based differences in biology. Recent research on cardiovascular disease (CVD), osteoporosis and depression has identified significant differences among women and men with respect to the distribution of certain diseases. Women and men have different sex- and gender-related risks for developing certain conditions and responses to treatment. For example, biological differences between males and females can affect how a medicine works in the body. Additionally, patterns of gene expression differ between males and females.

These sex and gender differences have important implications for health and healthcare. Thus, it is imperative to target medicines to these patient population sub-groups by utilising the correlation between sex and the incidence, prevalence, symptoms, age at onset and severity of disease as well as the reaction to medicines.

Yet, women are generally under-represented in clinical trials. Since the Thalidomide tragedy in the late 1950s there has been a reluctance to include women of childbearing age in clinical trials. *"The general assumption prevailed that women did not differ from men except where their reproductive organs were concerned and data obtained from clinical research involving men could simply be extrapolated to women."*<sup>1</sup> An article in the Nature journal argues that gender inequalities in biomedical research are undermining patient care and the article calls for the *"sex bias in basic research and clinical medicine to end."*<sup>2</sup>

Moreover, there is a particular lack of information on the safe use of medication during pregnancy and lactation. Most of the 5 million babies born in Europe every year have been exposed to medication(s) taken by their mothers during the pregnancy. More accurate epidemiological estimates in Europe today do not exist, unlike in the USA. Yet, the issue of medicines in pregnancy has been ignored in research, public health and regulatory policy and there is little information or advice available to pregnant women and their healthcare professionals. Today, however, the incidence of chronic diseases diagnosed pre-pregnancy continues to rise as women postpone pregnancy until a later date, as do age and Body Mass Index (BMI) at conception. Each of these contributes to worse outcomes for both mother and child. There is an urgent need for action to establish the safe use of medicines during pregnancy through a robust and comprehensive pharmacovigilance system.

### Regulating Medicines in Europe

The European Medicines Agency (EMA) is the European Union (EU) body responsible for the scientific evaluation and approval of medicines developed by pharmaceutical companies. The EMA centrally reviews and approves innovative medicinal products, based on the clinical trial data supplied by the applicant organisation/pharmaceutical company. This approval process is strictly defined and guided by EU legislation. Once approved, the medicinal product receives a marketing authorisation for use in the EU and European Economic Area (EEA).

The recently adopted **EU Clinical Trial Regulation No 536/2014** aims to create an environment that is favourable to conducting clinical trials in the EU with the highest standards of ethical and safety protection for participants. The new CT Regulation, which replaces Directive 2001/20/EC, was adopted in April 2014 and will become law in May 2016. This Regulation sets out the legal conditions under which clinical trials will have to be conducted in Europe in the future and includes many new provisions that will improve the inclusion of sex and gender in medicines regulation.

Firstly, the new Regulation is a major step forward in increasing clinical trial data **transparency**. It will improve the evidence-base on which a medicine has been approved for different population groups, such as women and older people. All clinical trials in the EU will need to be registered in a Clinical Trial Data base and a user-friendly summary of results must be published within one year after the trial has ended. Once a clinical study report has been submitted in support of a marketing authorisation, it will also have to be made publicly available by the applicant within 30 days after the regulatory decision has been made.

Secondly, in terms of demographics, the new Regulation lists **specific population groups** to be included in clinical trial, *"Unless otherwise justified in the protocol, the subjects participating in a clinical trial should represent the population groups, for example gender and age groups, that are likely to use the medicinal product investigated in the clinical trial"* and *"non-inclusion has to be justified."*

Thirdly, women who have chronic conditions such as asthma, diabetes and HIV/AIDS are often unsure of safety of medicines during pregnancy and breastfeeding as most medicines are contra-indicated or used off-label during pregnancy. The Regulation contains new legal provisions for including and **protecting pregnant and breastfeeding women** in clinical trials. Article 33, Chapter V defines the conditions under which pregnant or breastfeeding women can participate in clinical trials, provided the conditions outlined in the legislation are followed.

Fourthly, analysis of results according to Sex and Age Annex IV refers to **presenting sex and age differences** in the clinical trial results, “*population of subjects (information with actual number of subjects included in the clinical trial in the Member States concerned, in the Union and in third countries; age group breakdown, gender breakdown*” and under Section C, point 1 and 2 “*baseline characteristics (required) age, and gender.*”

### Examples of Good Practice

#### Ethics Committee Guidelines at the Medical University of Vienna

Ethics Committees play an important role in protecting the health and well-being of clinical trial participants. However, Ethics remains a national issue and can, therefore, not be harmonized by the EU CT Regulation. Since a primary aim of clinical research is to provide scientific evidence leading to improved standard of care, it is important to determine whether the intervention or therapy being studied affects women or men differently. The Ethics Committee of the Medical University of Vienna has drafted Guidelines that both genders should be included in all biomedical and behavioural research projects involving human subjects in scientifically appropriate numbers. Women of childbearing potential should not be routinely excluded from participation in clinical research, but appropriate measures to exclude potential foetal damage must be taken. Patients of both genders should be included in the same trials, if possible in numbers adequate to allow detection of clinically significant sex-related differences in drug response. If one gender is excluded, the reason must be clearly stated in the study protocol. One gender can be excluded because one of the following applies: 1. research question is relevant to only one gender; 2. prior evidence strongly suggests no gender difference; 3. data exists for excluded gender; or 4. subject selection is constrained due to purpose of the research. Cost is not an acceptable reason for exclusion.

#### Best Practice in the United States

##### NIH Revitalization Act

As far back as 1993, the National Institutes of Health (NIH) in the United States addressed the exclusion of women from biomedical and clinical studies through the NIH Revitalization Act, which called for women and minorities to be included in all human subject research in adequate numbers to allow for valid analyses in phase III clinical trials. The NIH explicitly stated that cost was not an acceptable reason for excluding women and minorities. In order to receive NIH funding, researchers have to explain how they address the gender issue.

##### Office of Women’s Health

The U.S. Food and Drug Administration (FDA) has its own Office of Women’s Health (OWR) to protect and support the health of women through policy and science. The OWR advocates for the participation of women in clinical trials and for sex, gender and sub-population analysis.

The FDA produced guidelines to ensure that women will be appropriately represented in clinical trials, amending its previous policy of excluding most women of childbearing age to participate in early phases of clinical trials. The FDA requires sponsors to include a fair representation of both sexes as participants in clinical trials, so clinically-related differences in response can be detected. The guidelines state that sponsors should collect gender-related data during research and development and analyse the data for gender effects in addition to the other variables of age and race.<sup>3</sup>

##### FDA Drug Trial Snapshots

The FDA Action Plan, published in 2014, sets out important steps for making clinical trial data across the demographic spectrum of sex, race/ethnicity and age more transparent and publicly available. It reflects the FDA’s commitment to encourage the inclusion and greater representation of a diverse patient population in biomedical research leading to the development of medicinal products that meet the real life health needs of patients. The Action Plan asks for subgroup data to be analysed, thus ensuring the safety and effectiveness of the medicinal product in a wider population.

The Snapshot initiative is part the Action Plan to make demographic subgroup data more widely available. Starting in 2015, based on the feedback received, FDA posts a Snapshot for every new medicinal product it approves. The Snapshots provide easy to understand information at a glance: including demographic breakdown by sex, age, and ethnicity and providing efficacy and safety results sorted demographically.

However, FDA cautions that “*Stand-alone conclusions regarding the efficacy and safety among different sex, race, and age groups could not always be made, usually because the numbers of patients in some groups were too low to allow for a meaningful comparison to the overall result. Therefore, interpretations of subgroup data must be made with caution, because findings in one direction or another are often inconclusive.*” Thus, some challenges must still be addressed in order to obtain statistically relevant and meaningful data for health professionals and patients.<sup>4</sup>

### Health Canada Guidance Document

In 2013, Health Canada issued a Guidance document to address the under representation of women in clinical trials. The guidance sets out “*considerations pertaining to the appropriate inclusion of women in all stages of clinical trials and research with the aim of identifying and analyzing sex-related differences that may affect the safety and efficacy of a therapeutic product.*” Health Canada argue that “*analysis of clinical trial data by sex may identify clinically relevant sex differences in therapeutic response and, as a result, minimize the risks, maximize benefits and promote the optimal use of therapeutic products in both women and men*”. It states that if data from early phase trials do not indicate potential sex-related differences, it cannot be assumed that clinically relevant differences do not exist.

The Guidance document, therefore, recommends that the statistical section of the study protocol for Phase III trials include pre-specific plans for asserting sex related differences. The Guidance document also includes provisions for including pregnant and breastfeeding women.<sup>5</sup>

### References

1. Health Canada. Considerations for Inclusion of Women in Clinical Trials and Analysis of Data by Sex—2013 Guidance Document
2. Nature. Vol 465, Issue no 7299, 10 June 2010
3. <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126835.pdf>
4. <http://www.fda.gov/Drugs/InformationOnDrugs/ucm412998.htm>
5. [http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/womct\\_femec-eng.ph](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/womct_femec-eng.ph)

## Steps for Action

1. Given that the scientific knowledge on sex differences is now well known and a more supportive legislative environment in Europe is about to come into force, the time has come to address remaining barriers and move from the description of sex differences to a more systematic approach of implementation into regulatory and clinical practice for the benefit of patients and, ultimately, to improve health and healthcare for all. Expert discussions in two workshops and the final Roadmap conference agreed on the following recommendations for improving medicines regulation in Europe:
2. Ethics Committees should develop guidelines that require the inclusion of women in clinical research, utilising insight from good practice example from the Medical University of Vienna.
3. The European Medicines Agency (EMA) should follow the FDA Snapshot initiative by making sex-specific data more readily available and transparent.
4. A new IMI-2 initiative should be created that brings together, researchers, industry, EMA and other key stakeholders to analyse existing barriers for the recruitment and retention of women and older people in clinical trials and to develop a robust methodology for subgroup analysis to prevent slowing down the regulatory process.
5. Rigorous sex- and age-specific pharmacovigilance reporting should be improved.
6. Robust post-marketing data for pregnant women should be collected and common rules for pregnancy exposure registries should be developed.
7. The European Medicines Agency together with key stakeholder should draft dedicated guidelines on sex and gender analysis of differences in clinical trials along the lines of Health Canada.

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