

### EUGenMed Expert Workshop

4 March 2015, European Economic and Social Committee, Brussels, Belgium

*Translating the evidence from S&G research into regulatory practice will lead to more targeted, effective opportunities for prevention, treatment and care. This workshop examined how S&G consideration are integrated into Medicines Regulation and information.*



#### Co-Chairs

Dr. Ingrid Klingmann, Chairwoman, European Forum for Good Clinical Practice (EFGCP)

Ms. Hildrun Sundseth, President, European Institute of Women's Health (EIWH)

#### Executive Summary

As part of the FP7-funded European Gender Medicine (EUGenMed) Project, the European Institute of Women's Health (EIWH) organised a workshop on 4 March 2015, bringing together a multidisciplinary, multi-sectorial group of experts to discuss *Sex and Gender in Medicines Regulation and Medical Education*.

Dr. **Ingrid Klingmann**, of the European Forum for Good Clinical Practice (EFGCP) and **Hildrun Sundseth**, President of the EIWH opened and co-hosted the morning session exploring Sex and Gender in Medicines Regulation. Dr. Klingmann explained the need for the event, "There is not enough data on 50% of the population—on women."



During the morning session, experts presented important issues around sex and gender in medicines regulation. Dr. **Kevin Blake** of the European Medicines Agency (EMA) explained how Sex and Gender issues are currently addressed in EU Regulatory practice and how in future the new EU Clinical Trials Regulation and Pharmacovigilance initiative will generate more evidence how medicines work in different patient population groups, such as in women.

Prof. Dr. **Marco Stramba-Badiale** of the IRCCS Istituto Auxologico Italiano, a leading expert in cardiovascular disease (CVD) in women, provided evidence how in the past women have often been underrepresented in CVD clinical trials and when they were included, the data had not been analysed. He was followed by Dr. **Christiane Druml**, Vice Rector of the Medical University of Vienna, who presented the University's Ethical Guidelines for including women in clinical trials.

Dr. **Fabio D'Atri**, Deputy Head of Unit of the European Commission, DG SANTE, the Directorate responsible for pharmaceuticals explained the New Clinical Trials Regulation and how in future its legal provisions will provide increased transparency of clinical trials data, including the population groups for whom the medicines are intended (gender, age). He explained that the legislation also provides new rules for including pregnant and breastfeeding women in clinical trials under strict protective measures. Dr. **Lode Dewulf** of UCB pointed out the lack of data and information on the safe use of medicines during pregnancy, despite 60 to 80% of women taking medicines during pregnancy.

EIWH Board Member and EUGenMed Project Partner from Maastricht University Prof. **Ineke Klinge** outlined the work of the EUGenMed research project, whose aim was to produce a Roadmap to collect the evidence for integrating sex and gender into biomedical, public health and clinical research and practice. Dr. **Ute Seeland** of the Institute of Gender Medicine at Charité—Universitätsmedizin presented the research evidence for integrating sex and gender into clinical studies, specifically the CVD differences between men and women.



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## Executive Summary (continued)

Finally, from the patients' perspective, **Sophie Peresson** of the International Diabetes Federation European Region, **Laurène Souchet** of the European Patients' Forum welcomed the EUGenMed project for providing more clinical data information for all patients. Dr. **Katrín Fjeldsted**, the President of CPME, spoke on behalf of medical professionals in support of ensuring that medicines regulation accounts for sex and gender differences.

Wrapping up the morning session, President of the EIWH, **Hildrun Sundseth**, stated, "*Translating the evidence from S&G research into regulatory practice will lead to more targeted, effective opportunities for prevention, treatment and care,*" and in recognition of the International Women's Day 2015, called on all stakeholders to follow this year's theme of "*Make It Happen*" in order to advance the evidence base for women.

## Welcome from the European Economic and Social Committee

*Ms. Ingrid Kössler, Member of the European Economic and Social Committee (EESC)*

Ms. Kössler stated that the EESC was established by the Treaty of Rome in 1957. Over the years, the EESC's role as intermediary between organised civil society and EU decision-makers has been strengthened. It is a consultative body that represents civil society and thus the people on the ground who are most directly affected by EU legislation. It has three main tasks: 1. To ensure that EU policies reflect the true economic, social and civic picture; 2. To build a more participatory EU, closer to its citizens, and 3. to promote EU values and civil society organisations globally.



The EESC is an assembly of 353 members from the 28 Member States of the EU and works in all 24 official languages of the EU. The EESC allows Europe's interest groups to have a formal and institutionalised impact on draft EU legislation by covering all topics affecting people's daily lives. Ms. Kössler went on to give an example of the promotion of gender equality in Sweden by the **1.6 Million Club**, a non-profit organisation that aims to raise awareness and spread information concerning women's health and lifestyle issue. The club was founded in 1998 by Alexandra Charles to fight male dominated science and the discrimination of women in health care. The 1.6 Million Club was formed to disseminate information from a female perspective. The name came derived from the 1.6 million women over 45 years of age in Sweden at the time of its inception.

## Sex and Gender in EU Regulatory Practice

*Dr. Kevin Blake, European Medicines Agency (EMA)*

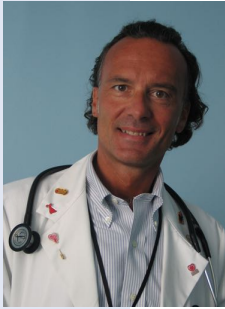
The importance of representation of both genders in clinical trials is acknowledged. However, in general, traditionally there has been an underrepresentation of women in clinical trials. Anecdotally, women may be more difficult to recruit and retain due to economic issues as well as the family/carer role.



Going forward, it may not be that representation in trials is exactly equal however the numbers of participants should be such that subgroup analyses are adequately powered to allow for meaningful conclusions on gender that can then be reflected in the product information. The new Clinical Trials Regulation is a major step forward in improving the evidence-base on which a medicine has been approved for different population groups, such as women and making clinical trial data more transparent. In addition, the new pharmacovigilance legislation and the 2014 Delegated Regulation on post-authorisation efficacy studies provide a firm legal basis to gather new and additional evidence where well-reasoned scientific uncertainty on efficacy exists for population subgroups including gender. All this leads to generation of new data and information to improve knowledge, which should be reflected in the publically available information on medicines to ensure their safe and effective use.

Dr. Blake discussed the importance of identifying knowledge gaps for certain population groups such as elderly women: the majority of older, multi-morbid patients; pregnant and lactating women; and sex-genetically linked issues in which there are not sufficient sample sizes to detect. He explained the need for systematic process for collection of pregnancy data as the percentage of women using medicines during pregnancy varies but can reach over 80%. There is some evidence that the use of prescription medicines may actually increase during pregnancy, primarily for the treatment of pregnancy-related symptoms. However, most medicines are not approved for use during pregnancy (56% to 100% of centrally approved medicines, depending on therapeutic areas). The new legislative framework supports the collection of such important data.

## The Case of Cardiovascular Diseases and Women



*Prof. Dr. Marco Stramba-Badiale, Director, Department of Geriatrics and Cardiovascular Medicine, IRCCS Istituto Auxologico Italiano, Milan, Italy*

Prof. Dr. Marco Stramba-Badiale explained that cardiovascular diseases are the leading causes of death in both men and women. Gender differences in the clinical presentation of cardiovascular diseases have been demonstrated, and some therapeutic options may not be equally effective and safe in men and women. Furthermore, sex differences in pharmacokinetics, pharmacodynamics and physiology may contribute to a different response to cardiovascular drugs in women when compared with men. Accordingly, preventive and therapeutic interventions should be tested in populations that fairly represent the gender distribution for each specific clinical condition or group at risk. *“In a project funded by the European Commission, we have demonstrated that the percentage of women enrolled in cardiovascular clinical trials is 33%. In only 50% of these trials, an analysis of the results by gender has been performed.”* Thus, women are under-represented in randomised clinical trials and the majority of therapeutic interventions are tested for safety and efficacy in male populations.

The reasons for the under-representation of women in clinical trials may be the lower occurrence of outcomes in females, which may affect the costs of the study; the lower willingness of women to be enrolled, due to their misperception of risk of cardiovascular diseases; and the difficulties in terms of transportation or support for the follow-up visits. Clinical trials enrolling a significant proportion of women to allow for pre-specified gender analysis should be conducted. Enrollment criteria and follow-up duration should allow for the inclusion of women at risk of developing cardiac events. A minimum enrollment for women should be ensured (e.g. maintain open enrollment for women until pre-specified proportion is reached). Prof. Dr. Marco Stramba-Badiale went on to say that the external barriers to the enrollment of women in clinical trials need to be addressed, and in particular, the transportation difficulties for follow-up visits. Finally, regulatory agencies are urged to adopt strict rules on the inclusion of women in clinical trials and a systematic gender analysis. Scientific societies, patients' associations and medical product industries should cooperate with European institutions, national health care authorities and regulatory agencies to promote scientific research on gender issues in cardiovascular medicine and a larger representation of women in clinical trials.

## Ethics Committee Guidelines—An Example from the Medical University of Vienna



*Dr. Christiane Druml, Vice-Rector, Medical University of Vienna, Austria*

Dr. Druml discussed the guidelines regarding the inclusion of women in clinical research at the Medical University of Vienna in 2004. Since a primary aim of clinical research is to provide scientific evidence leading to improve standard of care and/or a change in health policy, 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.

## Moving Forward: The New Clinical Trials Regulation

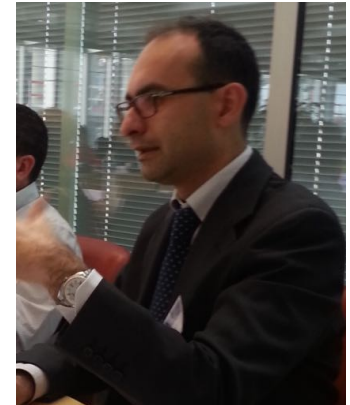
*Dr. Fabio D'Atri, Medicinal Products—Quality, Safety and Efficacy Unit, DG SANTE*

Mr. Fabio D'Atri, Deputy Head of Unit in Directorate General Health and Food Safety, gave an overview of the main provisions of new regulation on clinical trials.

In particular, he explained that in the protocol, a description of the group/subgroups participating in the trial has to be given together with a justification for the gender and age allocation of subjects. Furthermore, if a specific gender or age group is excluded from the trial, the reasons have to be given.

He also explained that the assessors of a clinical trial application will have to have a specific expertise if the trial is designed for a specific population group, such as the new provisions to facilitate the conduct of clinical trials and to collect data in pregnant and breastfeeding women.

Finally, he presented the main features of the future EU portal and EU database under preparation by the European Medicines Agency, which will greatly increase the transparency and information concerning clinical trials in Europe.



## Safe Use of Medicines during Pregnancy and Lactation

*Dr. Lode Dewulf, Chief Patient Affairs Officer, UCB, Belgium*

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, where the actual percentage of such exposure is known to be up to 90%. Ever since the thalidomide tragedy around 1960, the issue of medicines in pregnancy has been ignored in research and public health policy. Today, however, the incidence of chronic diseases diagnosed pre-pregnancy continues to rise, as do age and Body Mass Index (BMI) at conception. Each of these contributes to worse outcomes for both mothers and children. Thus, the use of medicines during pregnancy can no longer be simplified to non-use.



Changing the visibility and language around the issue is a first and necessary step: informed decisions around medicines and pregnancy should be the common goal. Even today, decisions can already become much more informed by improving access to and distribution of valuable information that already exists. Leveraging the Internet correctly is a way to do this with both speed and great impact. A quality seal for reliable information on the internet and a pan-European multi-stakeholder dedicated website are both options that would reduce the confusion caused today by an abundance of unclear, conflicting and unbalanced information currently on the web. New and more quality information is the next step.

When it comes to medicines that are still in clinical studies, some simple measures can ensure that we learn more from unplanned cases of pregnancy occurring during a study. From a societal perspective, however, the medicines used most frequently in pregnancy are not new and (thus) not subject to clinical studies any more. Here we need to increase the reporting of real-life pregnancies and their outcomes. Many mothers already use health or pregnancy apps and these should be leveraged as data source. For prescribers and dispensers, a safe harbor legal setting will reduce the reluctance to report what today is still “off label” medication use, and a standard reporting template for pregnancy will allow us to gain more knowledge from these cases. Progress on an issue as complex as this requires collaboration between all stakeholders and official EU funding support for data collection.

## EUGenMed—The Research Evidence for Integrating Sex and Gender into Clinical Studies



*Prof. Dr. Ineke Klinge, Maastricht University and Charité Universitätsmedizin, Berlin and EIWH Board Member, the Netherlands*

Ineke Klinge presented an overview of the full EUGenMed project. She introduced the partners and presented the rationale of the project. She gave an overview of the work plan and timing of the various activities. After the kick-off meeting in April 2014, four workshops were held from December 2014 to March 2015. Finally, she gave a preview of the structure of the roadmap to be presented at the final conference on 30 June in Brussels.

*Dr. Med. Ute Seeland, Institute of Gender Medicine, Charité—Universitätsmedizin, Germany* Dr. Seeland presented examples of basic research findings on cardiovascular diseases and gender, including its various clinical manifestations. She summarised the evidence of sex and gender differences in cardiology that should be considered for future guideline development. She discussed the research evidence and the need to integrate sex and gender into medicines regulation.



### Patient Perspective



*Ms. Sophie Peresson, International Diabetes Federation European Region*

Ms. Peresson presented the interaction of diabetes and pregnancy. Women with Type 1 and Type 2 diabetes are more vulnerable to complications, including to cardiovascular disease (CVD). There is a unique burden of diabetes affecting both woman and the unborn child. The rates of diabetes in pregnancy have increased in recent years due to rising obesity rates among the general population and due to the increasing number of pregnancies among older women. Gestational diabetes only occurs in pregnancy, when the body cannot produce sufficient extra insulin to meet the demands of pregnancy. Gestational diabetes can occur at any stage of pregnancy, but is more common in the second half of pregnancy.

Women need to know that they are twice as likely to develop Type 2 diabetes later in life if they suffer from gestational diabetes.

*Ms. Laurene Souchet, European Patients' Forum*

The gender perspective is important to EPF, as they are committed to health equity and tackling discrimination. EPF collaborate closely with EIWH and EMHF, who are both associated members. EPF have raised gender issues in some of their position papers, including the position paper on clinical trials to flag up the sex and age imbalance of participants in clinical trials. Ms. Souchet concluded by saying that *“The implementation of the Revised Clinical Trials Regulation should be monitored closely to ensure a gender balance in clinical trials.”*



### Health Professional Perspective



*Dr. Katrín Fjeldsted, President, Standing Committee of European Doctors (CPME), Iceland*

Dr. Fjeldsted outlined the physician's perspective on integrating sex and gender into medicines regulation. She explained CPME's activities with regard to medicines regulations, such as Regulation No 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use and Regulation (EC) No 1901/2006 on medicinal products for paediatric use. Dr. Fjeldsted congratulated and supported the European Institute of Women's Health on its work in the field of gender equity in health. She stated that she would commit to preparing a position paper on S&G and present it to the CPME Board for approval.

## TOWARDS A EUROPEAN S&G ROADMAP: RECOMMENDATIONS

1. Ethics Committees to develop guidelines that require the inclusion of women in clinical research, utilising insight from good practice example from the Medical University of Vienna.
2. EMA to follow the FDA Snapshot initiative—making sex-specific data more readily available and transparent.
3. Suggest IMI-2 initiative bringing 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
4. Improve rigorous sex- and age-specific pharmacovigilance reporting.
5. Request collection of post-marketing data for pregnant women and develop common rules for pregnancy exposure registries.
6. The European Medicines Agency together with key stakeholder to draft dedicated guidelines on sex and gender analysis of differences in clinical trials along the lines of Health Canada.



### EUGenMed Project

Project: <http://eugenmed.eu>  
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