

## Results from Workshop 1.4B: Medicines Regulation

**Hildrun Sundseth**, President of the EIWH and co-chair of this session together with Dr Ingrid Klingmann, opened the session. Ms Sundseth explained that medicines regulation was an area in which Europe had historically struggled, but recently made some large strides to integrate sex and gender (S&G) into practice at national and European level, through legislation, such as the new Clinical Trials Regulation.

She then discussed the importance of considering S&G in medicines regulation. Medicines are safer and more effective for all when clinical research includes diverse population groups of all ages. There are sex differences of tissues and cells, every cell has a sex. Women metabolise medicines differently; Ms. Sundseth cited the example of Ambien, a sleeping drug for which the FDA halved the dose for women. Yet, despite the scientific evidence, women have been under-represented in many clinical trials, and if they are included, robust analysis is often lacking. Europe must ensure that the evidence from S&G research translates into regulatory practice in order to develop more targeted, effective opportunities for prevention, diagnosis, treatment and care for all.

Ms. Sundseth then summarised the expert workshop on medicines regulation, organised by the EIWH and which she had co-chaired with **Dr. Ingrid Klingmann**, chair of the European Forum for Good Clinical Practice (EFGCP), in Brussels in March 2015. This workshop had brought together over sixty experts in the field, who engaged in lively discussion to generate recommendations for the EUGenMed roadmap. Firstly, ethics committees should develop guidelines that address inclusion of women in clinical trials, following the good practice example from the Medical University of Vienna.<sup>1</sup> Experts further suggested research proposals for the Innovative Medicines Initiative (IMI) to develop robust methodology for subgroup analysis and also to address existing barriers for the recruitment and retention of women and older people in clinical trials. Moreover, in preparation of implementing the new Clinical Trials Regulation, the European Medicines Agency (EMA) together with key stakeholders should draft guidelines on S&G analysis in clinical trials along the examples of best practice from Health Canada<sup>2</sup> and the FDA Safety and Innovation Act's (SIA) request for demographic subgroup data and analysis.<sup>3</sup> Additionally, Europe should improve rigorous sex- and age-specific pharmacovigilance reporting for existing products. In order to address the current knowledge gap, a regulatory framework should be developed for safe use of medicines during pregnancy, which should include post-marketing data collection and common rules for pregnancy exposure registries. The experts also advised that EMA should follow the FDA Snapshot<sup>4</sup> example and make sex- and age-specific data more readily available and transparent.

**Dr. Thorsten Vetter**, Scientific Officer at the EMA, presented on sex and gender in EU regulatory practice. He summarised the findings of EMA's analysis on gender bias in 2004 and the reasons for under-representation of women in clinical trials. He explained that the importance of representation of both genders in clinical trials is acknowledged by the EMA. It may not be that representation is equal, but it needs to be scientifically meaningful;

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<sup>1</sup> Medical University of Vienna. *Guidelines for the Inclusion of Women in Clinical Research*.

<http://ethikkommission.meduniwien.ac.at/fileadmin/ethik/media/dokumente/merkblaetter/Guidelines-incl-women-research.doc>

<sup>2</sup> Health Canada. 2012. *Draft Guidance Document: Considerations for Inclusion of Women in Clinical Trials and Analysis of Data by Sex*. [http://www.hc-sc.gc.ca/dhp-mps/consultation/biolog/draft\\_iwct\\_ebauche\\_ifec/lett-eng.php](http://www.hc-sc.gc.ca/dhp-mps/consultation/biolog/draft_iwct_ebauche_ifec/lett-eng.php)

<sup>3</sup> FDA. 2013. *Collection, Analysis, and Availability of Demographic Subgroup Data for FDA-Approved Medical Products*.

<http://www.fda.gov/downloads/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/UCM365544.pdf>

<sup>4</sup> <http://www.fda.gov/Drugs/InformationOnDrugs/ucm412998.htm>

ideally, subgroup analyses should be adequately powered to allow for meaningful conclusions that can be reflected in the product information. Dr. Vetter then discussed how the Clinical Trial Regulation (EU) No 536/2014 is a major step forward in improving the evidence-base on which a medicine is approved for different population groups, such as women and making clinical trial data more transparent.<sup>5</sup> In addition, the new pharmacovigilance legislation and the 2014 Delegated Regulation on post-authorisation efficacy studies provide a firm legal basis to collect new and additional evidence. He explained that a new concept paper on guidance on good pharmacovigilance practices (GVP) in pregnancy and lactation is under preparation which is expected to be published for consultation in mid 2016.

All of these efforts, Dr. Vetter argued, will lead to improved knowledge, which should be reflected in the product information to ensure safe and effective use of medicines. As supported by a short question to the audience as to which are the key sources for gender related drug information in Europe, it appears that the medical and scientific communities are not well aware of the gender related information available from European Public Assessment Reports (EPAR) and Summaries of Product Characteristics (SmPC), which are available on the EMA website.<sup>6</sup> In the light of initiatives like the FDA snapshot, it will be important to raise awareness among European Healthcare Professionals assuring that available data on gender specific aspects of drug efficacy and safety are duly accessed and considered.

**Dr. Klingmann** emphasised that the Clinical Trials Regulation is another step to generate data disaggregated by age and sex but information is still needed on gender differences and how to motivate women to participate in clinical trials. Participants then engaged in a lively Q&A session with the expert panel. **Ms. Sundseth** called on patient organisations under their empowerment initiative to inform their members on the sex and gender differences in diseases and increase pressure on regulators and the medical profession for improved information. **Dr. Marco Stramba-Badiale** discussed recent analysis on the continued underrepresentation of women in clinical trials explaining that in 62 clinical trials on different cardiovascular disease medicines held from 2006 to 2009, only 33% of participants were women despite the high prevalence of these diseases in women. Regarding the representation of women in clinical trials, **Dr. Lode Dewulf** said that efforts are needed to increase their participation and stressed that these efforts should be based on better insights on the actual reasons why today women are less represented, which may differ significantly between indications and countries. He mentioned the EUPATI project that trains patients to become informed partners in clinical research. He also highlighted the importance of collecting post-marketing data and argued for the use of the social media to address the issues of gender and sex differences in the future, with the use of medicines in pregnancy being a prime example. **Dr. Angela Maas, Dr. Marek Glezerman and Dr. Ineke Klinge** debated the reasons for the under-representation of women in clinical trials.

Closing the session, **Dr. Klingmann** explained that clinical trials data is generated on a global basis, so cross-national solutions are needed particularly in areas related to women’s participation and the generation of pregnancy and lactation data.

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<sup>5</sup> Article 6 requires a representative population in clinical trials and justification if this is not the case. Article 10 pertains to the consideration of vulnerable populations. Annex I stipulates justification if sex and age groups are underrepresented, and Annex V, which requires lay summaries of clinical trial results that include a gender breakdown

<sup>6</sup> [http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/landing/epar\\_search.jsp&mid=WC0b01ac058001d124](http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124)