

From gender-specific medicine to personalized medicine: challenges and opportunities for life sciences

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The study of gender differences and the development of a gender-specific medicine represents a milestone in the progress of life sciences and an interesting perspective to further develop personalized or precision medicine.

Understanding the mechanisms by which gender-related differences and various determinants of health – starting with lifestyles (drinking, smoking, exercise, diet and weight) – can affect and interfere with biological and physiological processes, or the onset and evolution of many diseases and the outcomes of therapies helps improve the knowledge needed to develop increasingly personalized and targeted treatments.

With this in mind, Farmindustria and its member companies have long been committed to overcoming the old ‘androcentric’ mindset. Indeed, despite being subject to the same medical conditions, men and women present very different symptoms, disease progression and response to therapy.

Hence the need to dedicate special attention to gender research, by introducing this ‘new’ dimension into all areas of medicine, bearing in mind that the differences originate *in utero*: for example, the different quantity and distribution of adipose tissue, which is visible already from the third month of intrauterine life, condition the response to therapies that pass through the placenta and that, therefore, can have different effects on female and male fetuses.

In this context, also for the pharmaceutical industry, the study of women’s health is no longer limited to exclusively female pathologies of the breast, uterus and ovaries: it is part of gender-specific medicine that, along with the age factor, takes into account that a child is not a small adult, that a woman is not a copy of a man and that the elderly have characteristics that are different from those of the young.

Since medicine is not a neutral science, only by proceeding in this direction it will be possible to guarantee all individuals, men and women, therapeutic appropriateness, by further strengthening a patient-centred approach and treatment personalization. Considering gender a determinant of health helps guarantee both men and women the protection of their health and the best possible clinical, diagnostic and therapeutic approach.

Biomedical research in this field focuses in particular on those medical conditions that, while present in both women and men, differ in terms of their incidence, clinical characteristics and response to therapy, such as, for example, degenerative, metabolic, infectious, immune and oncological diseases.

For this reason, Farmindustria has welcomed Italian Law no. 3 of January 11, 2018, that makes the Italian Government responsible for reorganizing and reforming clinical trial regulation. Indeed article 1 introduces specific indications regarding a gender-specific medicine approach, by requiring clinical trials to be conducted with adequate gender representation and article 3 defines the implementation of gender-specific medicine in the Italian National Health Service.

Regulation (EU) 536/2014 on the clinical trial of medicinal products for human use, which is due to come into force in 2020, also focuses on gender representation in clinical trials and dedicates article 33 to clinical trials on pregnant and breastfeeding women.

Such legislative ‘attention’, which is consistent with the commitments undertaken by pharmaceutical companies, aims to overcome the gender prejudice that, together with other factors – fear of causing fetal damage, reluctance of women to participate in clinical studies, increased costs due to the higher number of subjects to be enrolled – has led in the past to limited enrolment of women in study protocols for medicinal product authorization.

However, enrolling more women is not enough. We also need to be able to statistically analyze the results by subpopulation (males, females), to pinpoint the ‘female variability’ that depends also on physiological hormonal changes, the use of sex hormones for contraception and the possible replacement therapies for the post-menopause period.

Great attention must also be dedicated to studying the greater frequency and severity of adverse events amongst female subjects (almost twice than that observed in men) due to a series of factors, such as polytherapy (more common in women); age (women prevail in the over-75 population); depression (more common in women); and a greater susceptibility to risk factors.

The World Health Organization (WHO) identifies gender as an essential element for the promotion of

health aimed at developing diversified treatment approaches for women and men and, therefore, for treatment personalization.

To achieve this kind of appropriateness, we also need to guide healthcare interventions, devise specific programs, organize training processes and adequately direct research.

Farindustria is convinced that the gender dimension in health is a methodological and analytical necessity that can become a tool for health governance and planning, also considering the important role it plays in the occupational risk assessment.

As a matter of fact, the exposure thresholds to specific risks (chemical, physical, biological, ergonomic and musculoskeletal overload), have traditionally been established in a neutral manner and, while extremely cautious, they may vary according to sex, genetic factors and lifestyles.

In this regard, it is important to point out that women's health disorders have changed according to their new roles in society. Having achieved new professional objectives is undoubtedly a great success for the female gender; but it must not be forgotten that in addition to work, very often women have to attend to all the domestic and caregiving activities. They reinforce the patient-centred approach and ensure home care as the qualitative and sustainable alternative to hospitalization, which is sometimes inappropriate. This responsibility overload is the reason why stress-related disorders have increased amongst women, with a consequent increase in cardiovascular diseases that, it is no coincidence, have become the first cause of death among women.

The commitment of pharmaceutical companies to research in general and to clinical studies on gender differences in particular has grown constantly in recent years: today, 42% of medicinal products under development are for precision medicine, a rate that rises to 73% if we consider cancer drugs alone. The enrolment of female subjects in clinical trials has therefore gone up, although we need to further increase women enrolment to definitively overcome 'gender prejudice'.

The focus on this subject is well consolidated both in Italy (Italian Ministry of Health, Italian Medicines Agency, Italian National Institute of Health, Scientific Societies) and internationally (FDA, EMA, WHO), so as in Farindustria.

Over the past few years, the Association has undertaken a number of initiatives, in partnership with different stakeholders, in order to increase information and training initiatives on this topic. Farindustria continues to guarantee its presence at events where this subject is tackled and discussed. It also cooperates with the Italian Pharmacology Society (SIF), with the other Scientific Societies and with the National Women's Health Monitoring Centre (ONDA) to publish volumes on gender-

specific pharmacology; it assigns awards to young female researchers on gender-specific medicine; and together with Trenitalia and Incontra Donna it organizes an initiative called "Freccia Rosa", making it possible for women to have free breast cancer screening on Frecciarossa trains.

No less important is the annual event — now at its fourth edition — organized by Farindustria on March 7, aimed at supporting women who take care of family members, often juggling caregiving with their jobs. This year, Farindustria signed a protocol of intent with Asogenerici and the Italian Occupational Medicine Society (SIML) to promote and improve the health of over 200 thousand people: the 66 thousand employees of pharmaceutical companies and their families.

This protocol goes beyond law obligations regarding occupational safety vigilance, transforming them into a broader opportunity. Together with occupational physicians, we run a joint prevention program addressing the health needs of each employee, by promoting screening, correct lifestyle education and information on chronic diseases. Occupational physicians thus become more than mere agents of a legal obligation, at times of a purely bureaucratic nature. They help men and women who work in pharmaceutical companies, to take better care of their own health within their different family situations.

These are actions that aim to achieve the ultimate goal of protecting health. They could be performed during the mandatory medical checkups or through specific initiatives such as seminars, dedicated campaigns and specific events (for example, on antibiotic resistance or vaccinations), organized by companies.

The pharmaceutical companies therefore promote diversity management, which should not be understood simply as gender diversity, but also as a diversity of needs, family situations, medical conditions, treatments and therapies.

These activities are carried out with great determination and passion and significantly characterize employment in pharmaceutical companies. Women account for 42% of employees, compared to 22% in the Italian economy as a whole. They occupy important roles in corporate organization: in the pharmaceutical sector, women occupy almost 40% of management and executive roles, more than in all other sectors of the Italian economy (19%). Furthermore, 52% of researchers are women.

Productivity depends on the quality of work, which in turn depends on the quality of life. This is something pharmaceutical companies are well aware of, which is why they offer their employees one of the most modern and effective examples of corporate welfare, with special benefits specifically for women: the possibility of requesting a longer period of maternity leave than that granted by the Italian National Labour Agreement, the chance to obtain smart-working conditions, flexible working hours,

supplementary health insurance that focuses in particular on preventive medicine for female diseases and special transport initiatives, to name but a few.

In order to achieve the targets set by personalized medicine, of which gender is the most relevant determinant, the commitment of the pharmaceutical industry alone is not enough. It is not sufficient to simply include more women in clinical trials in order to resolve the problems.

We need to devise a new governance able to promote scientific and research activities with a gender-specific perspective, to develop prevention initiatives and identify gender-specific risk factors in all areas of medicine and diagnosis and treatment protocols that are gender-defined and oriented, we need to train and educate healthcare professionals and to include gender aspects in the collection and processing of information flows and when preparing health budgets.

The advantages that guide current research on gender-specific medicine derive from a person-centred approach that focuses on the individual rather than the illness. Namely:

- better clinical trial design, due to the recruitment of responders rather than non-responders at the time of enrolment;
- rapid, early diagnosis with important repercussions on prevention based on the identification of markers, including genomic markers;
- increased treatment efficacy and safety, as treatments can be chosen on the basis of the specific characteristics of the patient (personalized medicine) and of the medical condition (precision medicine);
- lower incidence of adverse reactions;
- savings for the Italian Health Service, due partly to a reduction in direct and indirect costs, which are often generated by adverse drug reactions.

Ultimately, in accordance with the increasingly compelling scientific evidence, Farindustria believes that gender medicine may constitute not only the basis for promoting therapeutic appropriateness and building precision medicine designed to meet patients' specific needs, but also an appropriate response to make the clinical management of diseases more efficient to the advantage of National Health Service sustainability.

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Conflict of interest statement: the Author is the Director General of Farindustria.

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