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Proposal for a new regulation to integrate gender medicine into EMA's drug authorization process in Europe

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The recent legislation in Italy for the development of gender medicine (Law no. 3/2018)

With the promulgation of Law no. 3 of 11 January 2018,[1] also known as 'DDL Lorenzin', Italy was one of the first Countries in the world to adopt a legislation able to promote the development of gender specificities and parity in the health sector. This legislative step – carried out thanks to the collaboration of all national health institutions (Ministry of Health, ISS [*Istituto Superiore di Sanità*, 'National Institute of Health'], IRCCS [*Istituti di Ricovero e Cura a Carattere Scientifico*, 'Scientific Institutes for Research, Hospitalization and Health Care'], AIFA [Italian Medicines Agency] and AGENAS [*Agenzia Nazionale per i Servizi Sanitari Regionali*, 'National Agency for Regional Health Services']) and the participation of qualified representatives from the scientific and healthcare communities – will have important repercussions not only on the healthcare offer of our National Health Service, but also on the clinical trials of drugs. In fact, Art. 1 of the law provides for the adoption of measures useful for the reform of the current provisions on the clinical trials of medicinal products for human use, introducing a specific reference to gender medicine.

The WHO document "*Health 2020: A European policy framework…*"

The importance of the gender approach in healthcare, both for care and research, is also reported in the WHO document "*Health 2020: A European policy framework…*",[2] where gender is recognized as a determining factor of the health status of an individual, since it is closely related both to the differences between males and females due to biological and physiological factors (sex), and to the differences between men and women due to social, environmental and behavioral factors (gender). Therefore, in order to increase the appropriateness of care, it is essential to include the research activities in a gender perspective. For the development of new drugs, this translates into a more balanced selection by sex and gender of the study groups included in the clinical trials.[3]

Gender medicine in the clinical trials

To date, the need to balance the study groups by sex has been related to the presence of differences between males and females in terms of incidence, clinical characteristics and response to therapy. This need is, in fact, recognized within the regulation that underlies the conduct of clinical trials for medicines for human use, both European[4] and American.[5] Despite this, in a number of cases a scarce inclusion of women in clinical trials was noticed. This may have been due to several reasons, including women's reluctance to take part in trials during childbearing age or during pregnancy. Although this attitude may be valid in the early stages of drug testing – particularly in phase I, due to possible unknown teratogenic effects – it does not find any sound justifications in the later phases.

The imbalance in the inclusion of the two sexes in the trials has been the subject of a recent debate in the *New England Journal of Medicine*,[6] which emphasized that women were totally excluded from the DISCOVER trial,[7] carried out to verify the pre-exposure prophylactic action (PrEP, *Pre-Exposure Prophylaxis*, in subjects at risk of manifesting the HIV infection) of the tenofovir alafenamide + emtricitabine combination. This methodological choice, currently being approved by the FDA,[8] led to the exclusion of cisgender women from the registered indication, since the effects of vaginal mucus on the drug were unknown.[9] The lack of balance between the two sexes, however, does not occur exclusively against the female sex; for example, in several cases the trials with breast cancer drugs – although such disease affects less than 1% of the male sex – are conducted with the complete exclusion of the male sex from the study design,[10] so as to lead the FDA to produce a special recommendation to pharmaceutical companies to also include the male gender in these studies.[11] The examples mentioned, although extreme, underline how extremely important it is to ensure equity in the inclusion of the two sexes in the study designs, in order to ensure that the benefits and safety of the new medicinal products are adequately investigated before they become available on the market.

Gender medicine and the registration procedures of new drugs

However, the balance between the two sexes – which in most cases is taken into account in the later phases of drug development[12] – is not sufficient to ensure that the two genders are adequately represented in the trials. Hence the need to develop, through European Medicines Agency (EMA), drug registration regulatory procedures at European level able to also take into account gender differences.[13]

The new regulatory framework could be inspired by what has already been done at European level to promote the research on new pediatric medicines.[14] In fact, as described in the report on the state of the research for pediatric drugs 10 years after the entry into force of the new regulation,[15] the development of a system of obligations and incentives for the companies that implement pediatric study plans for their products has led to a real cultural change, capable of stimulating and making the pediatric population more visible within the development process of a drug. This has materialized with an increase in the products specifically indicated for the pediatric population and, above all, with a significant increase in the information on the correct use of the drugs in this population. Considering the positive results of this experience, the system of obligations and incentives could be adopted so as to also favor the inclusion of gender medicine as an integral part of the drug development plan, and therefore of the registration processes. For example, through an *ad hoc* regulation, based on previous rules,[16] an extension (for example 1 year) of the patent duration (Supplementary Protection Certificate reward) could be envisioned for the products which have also been studied within a gender perspective. This extension should be granted regardless of whether or not differences between the two sexes/genders have been identified. Such a measure, highly appreciated by pharmaceutical companies, could be the useful incentive to increase our knowledge about the possible gender differences deriving from the use of drugs.

Precision medicine and gender medicine

All this would translate into numerous advantages, both for the research itself and for the healthcare system. In fact, the integration of gender medicine within the development and registration plan of new drugs will make it possible to increase our knowledge on the effectiveness of medicines and, at the same time, to reduce the occurrence of adverse reactions, so as to achieve a greater appropriateness of care, with positive effects on the citizens' health and the sustainability of the healthcare system. In other words, a specially developed regulatory system will allow gender medicine to play an important role in the structural change that medicine is experiencing, that is, in the so-called "personalized and precision medicine".

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