Presidenza del Consiglio dei Ministri

ITALIAN NATIONAL BIOETHICS COMMITTEE

PHARMACOLOGICAL TRIALS ON WOMEN

28th November 2008

PRESENTATION

The National Bioethics Committee (NBC) in the plenary meeting of the 28th of November 2008 approved the Opinion "*Pharmacological Experimentation on Women"*.

This document, starting with the analysis of the data on clinical experimentation on women, highlights their under-representation in enlistment and the poorly differentiated processing of the results, with particular reference to pathologies that are not specifically female. It is highlighted that, although women are the largest consumers of medicines, the experimentation tends not to sufficiently consider their specific nature and the change in the conditions of women's health, with a consequent increase in side-effects when taking medicines. The document analyses the main reasons for this shortcoming, it discusses the ethical problems arising from it and analyses the international and national rules on the issue.

The NBC proposes bioethical guidelines for an equal consideration of women in experimentation, highlighting the need for a differentiation, showing the dangers of a "neutral" pharmacology with regards to sexual differences. Women cannot be assimilated to men, like a mere variable, but have a specificity that experimentation must take into consideration in order to promote a medicine that adequately recognises equal opportunities between men and women. In order to increase pharmacological experimentation that is differentiated by sex, the NBC suggests to raise awareness within health authorities and to motivate pharmaceutical companies to support experimentation that is differentiated by sex, even though it might not be very profitable, encouraging research programs on the subject; to promote the participation of women in clinical trials with adequate information on the social importance of the experimentation on women; to guarantee a greater number of women as experimenters and as members of ethical Committees; to urge healthcare training that pays greater attention to the female dimension in pharmacological experimentation, as well as in research and treatment; to increase international cooperation, as well as national and local cooperation, focusing on the female condition in clinical experimentation.

This text has been drafted by Prof. Laura Palazzani, coordinator of the working group, with the contributions of Prof. Silvio Garattini and of Dr. Laura Guidoni. Within the working group, Prof. Salvatore Amato, Prof. Luisella Battaglia, Prof. Adriano Bompiani, Prof. Cinzia Caporale, Prof. Francesco D'Agostino, Prof. Lorenzo d'Avack, Prof. Marianna Gensabella, Prof. Maria Luisa Di Pietro, Prof. Emma Fattorini, Prof. Carlo Flamigni, Prof. Assunta Morresi, Prof. Demetrio Neri, Prof. Andrea Nicolussi, Prof. Lucetta Scaraffia, Prof. Monica Toraldo di Francia, Prof. Giancarlo Umani Ronchi, Prof. Grazia Zuffa and Dr. Riccardo Di Segni participated to the discussion. During the meetings of the working group, the Presentations of Prof. Flavia Franconi, Prof Matilde Leonardi and Prof Carlo Tomino, offered important contributions.

In the plenary meeting of the 28th of November 2008, the Opinion received the consensus of those present (Prof. Salvatore Amato, Prof. Stefano Canestrari, Prof. Antonio Da Re, Prof. Lorenzo d'Avack, Prof. Carlo Flamigni, Prof. Silvio Garattini, Prof. Marianna Gensabella Furnari, Prof. Laura Guidoni, Prof. Assunta Morresi, Prof.

Demetrio Neri, Prof. Andrea Nicolussi, Prof. Laura Palazzani, Prof. Alberto Piazza, Prof. Lucetta Scaraffia, Prof. Monica Toraldo di Francia, Prof. Giancarlo Umani Ronchi and Dr. Riccardo Di Segni), with the abstention of Prof. Adriano Bompiani, Prof. Roberto Colombo, Prof. Francesco D'Agostino, Prof. Bruno Dallapiccola, Prof. Maria Luisa Di Pietro, Prof. Emma Fattorini.
Prof. Adriano Bompiani, Prof. Bruno Dallapiccola, Prof. Maria Luisa Di Pietro, Prof. Rodolfo Proietti clarified their abstention with additional note, cited at the end of the text.
Prof. Luisella Battaglia, Prof. Romano Forleo, Prof. Claudia Mancina, Prof. Vittorio Possenti and Prof. Grazia Zuffa, absent from the meeting, expressed their agreement.

Rome, 28th November 2008

The President
Prof. Francesco Paolo Casavola

1.Introduction

Recent studies highlight how women, in today's society, have a longer life expectancy in comparison to men in the same socio-economic circumstances, but their life seems to have "less health"[1]. An apparent paradox – women live longer, but with more health problems in comparison to men – it can be explained also on the basis that the conditions of health and illness depend on complex relationships between the biological dimension, the psychic as well as symbolic component and the historical-social-cultural influences. The changes that women have lived through and are still living through are profound, especially in western civilizations, with consequent changes regarding the relationship between health and illness. Some illnesses traditionally considered typical of the male population are now statistically more widespread in women, but medicine – in some of the specializations in which it is developed – does not seem to take into adequate account such changes in their policies of prevention, diagnosis and cure.

Biomedical research – in general and in past decades – tended to reflect predominantly a male perspective, according to some, assimilating women to men (except in some particular specializations): many researchers and doctors in some fields of human pathology have not adequately taken into account sexual differences with regards to the study of the symptoms, the assessment of the diagnosis and the efficacy of the treatments. The lack of consideration of sexual differences is part of a research that tends to the generalisation of any organic phenomenon (although this is necessary), not always paying enough attention to differences due to sex, as well as those due to age (taking into account under-age patients[2] and the elderly), disability and ethnicity.

However it is fair to indicate that not only a more "mature" clinic, but also a more careful research, have in recent time offered, and continue to offer more and more today, examples of greater balance in the formulation of protocols and the relative "enlistments" of the subjects.

Medicine's "neutral" approach, "in-different" to sex differences, has come to light for a long time in the experimentation of medicines, for reasons that will be subsequently clarified. As a consequence, although on one hand we highlight an increase in the consumption of medicines by women in comparison to men[3], on the other hand it appears

[1] This is true in almost all Countries although there are great differences in the life expectancy of men and women. A. Barford, D. Dorling, G Davey Smith, M. Shaw, *Life Expectancy: Women Now on Top Everywhere*, "British Medical Journal", 2006, 332, p. 808.

[2] On this topic cf Regulation (CE) number 190/2006 of the European Parliament and of the Council of Europe regarding drugs for paediatric use, which ends the marketing of drugs tested almost exclusively on adult subjects.

[3] In Italy the greater consumption of drugs by women is per-capita data, therefore normalised. Cf. paragraph 5.

that the effects of drugs on women are less studied or not adequately studied with regard to female specificity[4]. Women are more exposed to possible side-effects when they take drugs after their introduction on the market and we highlight less efficacy in the use of the drugs, with more frequent unwanted side-effects, which are also more serious compared to those experienced by men[5].

It is a bioethical problem that has emerged in international literature, in particular in the United States. It must be taken into account that the Food and Drug Administration (FDA) currently has an office that takes care specifically of women's health and of their participation in clinical trials[6] (the CDs "clinical trials gender oriented")[7]. The European debate generally refers to the guidelines set by the United States; in Europe, until today, no National Bioethics Committee has chosen this theme as an object for reflection[8]. In Italy, studies regarding this field are still few, even if we can report recent initiatives in the direction of a greater consideration of the female specificity in pharmacological experimentation. In 2005 the Ministry of Health created the workbench on "Women's health and drugs for women" (with the participation of the Superior Institute for Health, of the Italian Drug Agency, of the Regional Health Service Agency and of the Italian Society of Pharmacology). In 2007 a working group was created "Gender approach to health" within the Women's Health Commission, part of the Ministry of Health, with the primary objective of implementing the gathering of statistical data about female health, of promoting research and training in this field. In 2008, the Report on the "State of women's health in Italy" was published, which, in the context of the general consideration of female health, also touches on the problem of drugs. Also in 2008, the Italian Drug Agency (IDA) introduced the equality between men and women as one of the criteria of the Evaluation of the Agreements' Plan Commission to assign funds to industries which invest in Italy in pharmacological research. The Italian Society of Pharmacology (ISP) has in recent years started a working group that has the objective of motivating pharmacological research on sexual differences, through a campaign of information aimed at health workers, with the purpose of boosting the formation of experts in this sector and to raise awareness in health authorities.

Awareness is growing – at a time in which we are trying to achieve the individualization of the cure, working on the genetic or immunity component – that the analysis of the data stratified by sex can give indications on the best therapy to follow and supply useful information for deeper studies with a scientific basis on the illnesses that

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[4] E. Annandale, K. Hunt, *Gender Inequalities in Health*, Open University Press, Buckingham 2000; F. Franconi, S. Canu, I. Campasi, working group "Approccio di genere alla salute", *Approccio di genere nella ricerca, nelle sperimentazioni e nei trattamenti farmacologici*, in *Lo Stato di Salute delle donne in Italia. Primo rapporto sui lavori della Commissione Salute delle Donne*, Rome 2008, pages 39-53.

[5] Cf. paragraph 5.

[6] Cf. http://www.fda.gov/womens/trials.html. In some North American Universities, like the Columbia University in New York, there are activities entirely dedicated to these problems. In the last few years the publication "Gender Medicine" has published research aimed at highlighting the differences in the physiology, in the physiopathology or in the way the drugs respond. Even congresses on the topic are growing (htpp://www.gendercongress.com/).

[7] We clarify that in this document the use of the expression "gender" refers to the sexual difference between men and women. This is not the place to tackle the problem of the identity of gender and of other meanings of the expression, on which the NBC intends to return in another document.

[8] In the same month and year, the Austrian Committee for Bioethics issued "Recommendations with Gender Reference for Ethics Committees and Clinical Studies (15th November 2009),

affect both men and women. Adequate participation of women in experimentation, would allow us to understand if in therapies there are significant differences that can be attributed to sex, even to be able to consider the different incidence or relapse of the pathology.
The NBC has already looked at the general problem in pharmacological experimentation (*The experimentation of drugs*, 17th November 1992), but has not specifically analysed this problem in reference to women. The objective of this document is to reflect on the current state of pharmacological experimentation within sexual difference and on emerging bioethical problems, aiming to avoid any form of discrimination and to promote sexual equality in healthcare.

In here, the document does not intend to look at the problem of the pharmacological experimentation on pregnant women, reserving the right to discuss the topic in a future document[9].

2. *Clinical experimentation*

When we speak of clinical trial, we generally refer to the process of verification of the safety and efficacy of a medicine in relation to therapeutic properties after a phase of laboratory research and pre-clinical experimentation on appropriate subjects. Clinical trial can in reality involve other therapeutic instruments, different from drugs, like medical devices, or diagnostic instruments, including genetic tests. However, as both the regulations and the ethical approach have essentially been developed for drugs, generally we refer to this sector of biomedical research, eventually transferring to the other sectors the models and the procedures that have been developed, especially with regard to the protection of the patients.

Clinical experimentation in order to develop new drugs in Italy, as in the rest of Europe, takes place with common methods, through various experimental phases, in accordance with the norms of "Good Clinical Practices"[10]. This allows homogeneity from a scientific point of view as well as from an ethical point of view, with regards to the respect due to the rights of the patients involved. The regulations make provisions for the verification of the safety and the efficacy of the new drugs before their introduction on the market. This verification applies the methods of evidence based medicine (EBM), which at the moment is considered the most adequate model to guarantee that the introduction of new drugs will benefit the greatest amount of patients. We must remember that this is not the only possible model, but it is the one that is generally considered the most suitable because of the needs of modern medicine and because of its impact on the population's health.
Drugs' experimentation, before the authorisation to market them, makes provisions, after the pre-clinical phase, for phase I, essentially about safety, and phases II and III, in which

[9] With regards to experimentation which is not directly therapeutic in the interest of the pregnant woman or of the breast feeder, aiming to achieve effective protection of the health of the woman, of the embryo and of the foetus, and of the child after birth, the additional conditions anticipated in ch. VI of article 18 of the additional Protocol to the Convention of human rights and biomedicine are applied, relative to biomedical research, approved in Strasbourgh on the 25th of January 2005, which indicate particular precautions.
[10] The "Good Clinical Practices" constitute an international standard of ethics and quality of planning, managing and recording clinical studies. In Italy they were first adopted as part of the national legislation with the ministerial decree of the 15th of July 1997.

the efficacy of the drug on a growing number of patients is established. Subsequently the drug is authorised by the health authorities and becomes part of the clinical practice. Other phase IV studies can take place, always with experimental characteristics and therefore with the enlistment of a certain number of patients, aimed at better establishing the efficacy of a new drug with regards to the safety of use, even for longer periods of time. The whole process is under the control of health authorities, primarily of the Italian Drug Agency (IDA), which is called to supervise and if necessary direct, through its funding, drug research[11].

3. *Clinical experimentation on women: under-representation in the enlistment and shortcomings in the differentiated analysis of the data*

Within clinical drugs experimentation, women appear to be "weak subjects", or at least they appear to be not subjected to adequate consideration, which should take into account their specificity both from a quantitative point of view (number of enlisted women in comparison to the number of men) and a qualitative point of view (analysis of the data with regards to sexual difference).

In Italy numerous studies are carried out *on female pathologies*: in this case the enlistment of the patients is determined by the pathology. Analysing the data reported by the IDA, we can see that on a total of 4,196 experimentations from 2000 to 2006, there is a progressive increase of studies specifically carried out on women (cf. tab.1). Analysing the data of these trials, what emerges is a greater attention to phases II and III, an absence of phase I and a scarce emphasis on phase IV (cf. tab. 2). But what emerges the most is that such experimentations are mostly dedicated to therapeutic strategies for female pathologies, like the breast cancer and the control of the post-menopausal osteoporosis[12]. Studies are also carried out on the genitourinary field, the musculoskeletal system, connective tissue, the endocrinal system, in the context of the pregnancy, the labour and the time immediately after giving birth and in the context of the disorders of the nervous system. There are many studies on female fertilization with regards to ovarian stimulation as well as assisted fecundation; others are aimed at controlling incontinence in post-menopausal women (cf. tab. 3)[13]. We highlight that there are specific trials on women in the field of cardiovascular pathologies especially after the menopause, thanks to national studies on the incidence of these illnesses, in which the data is stratified by sex as well as age[14]. There are areas in which we notice a lack of pharmacological trials on female pathologies as well: in particular with regards to the substitutive hormonal treatment in post-menopausal women, where there are many risks of heart attack or breast cancer or cardiovascular toxicity of the chemotherapy drugs used to treat breast cancer.

[11] Part of the IDA is the Observatory on drug experimentation, which collects the data of all the experimentation conducted in Italy, periodically published in their bulletins. The data of the Observatory can be found on http://oss-sper-clin.agenziafarmaco.it.

[12] J.E. Rossouw, G.L. Anderson, R.L. Prentice, A.Z. LaCroix, et al. (Group for the Women's Health Initiative Investigators), *Risks and Benefits of Estrogen plus Progestin in Healthy Postmenopausal Women*, "JAMA", 2002, 288, pages 321-332.

[13] On the site of the Observatory we can search for current studies, using the key word "women": the studies which specifically involve women, in relation to female pathologies, are almost 60.

[14] An example of this is the "CUORE" (heart) project, coordinated by the Higher Institute of Health.

The areas of criticality and disadvantage for women are highlighted, in particular, with regard to the experimentation of drugs *on pathologies that are not specifically and traditionally female*[15] (even if few data is reported, as confirmation of such lack of interest). The majority of trials do not allow for a difference between men and women at the moment of enlistment and of the analysis of the data. The percentage of women (if compared to that of men) recruited in the experimentation is still low: it is referred to as "representative inappropriateness" or "under-representation" of women[16]. Drug dosage is generally measured on men (70 Kg. in weight) and women are considered a "variation" of the male model: but the weight difference between men and women, as well as the morphological and physiological difference, determines a considerable difference in the pharmacokinetics, that is the different way in which the drug is absorbed, distributed, metabolised and eliminated, and in the pharmacodynamics, that is in the response of the body to a certain concentration of drug in the blood or in the tissue[17]. Despite the fact that the knowledge of the specificity of the female body has matured, experimentation protocols have not been modified, therefore the enlistment without distinction between men and women persists and so does a consequent undifferentiated analysis of the data. Women are generally included (if they are) in phase III of the enlistment in the trails, but not in phases I and II of the trails (important phases, as already mentioned, to establish dosage, side-effects and safety in the drug's use). The lack of specific studies on women, especially in the early phases of the research, does not make it possible to measure the real efficacy of the drugs on women, but could even have limited the identification of specifically female drugs (cf. tab. 4)[18].

4. *New needs of experimentation differentiated by sex: the changes of health/illness in women*

The fact that there's a lack of studies which take into account the sex difference within pharmacological experimentation, is even more problematic, given the recent change in the conditions of women's health/illness within the context of the general change in the female condition. Some of the illnesses considered "male", today tend to be more frequent in women.

There are many factors, as we know, that have contributed to a change in the conditions of women, at least with regard to western societies. We need to consider: the increase in education (in latest years women exceed men in the number of graduates and

[15] That is male/female pathologies.

[16] F. Franconi, S. Canu, I. Campasi, Working Group *"Approccio di genere alla salute". Approccio di genere nella ricerca, nelle sperimentazioni e nei trattamenti farmacologici*, cited.

[17] M. Anthony, M.J. Berg, *Biological and Molecular Mechanism for Sex Differences in Pharmacokinetics, Pharmacodynamics, and Pharmacogenetics: part I*, "Journal of Women's Health and Gender-Based Medicine", 2002, 11 (7), pages 601-615; M. Gandhi, F. Aweeka, R.M. Greenblatt, T. Blaschke, *Sex Differences in Pharmacokinetics and Pharmacodynamics*, "Ann. Rev. Pharmacol. Toxicol.", 2004, 44, pages 499-523, A.D.M. Kashuba, A.N. Nafzinger *Physiological Changes during the Menstrual Cycle and their Effects on the Pharmacokinetics and Pharmacodynamics of Drugs*, "Clinical Pharmacokinetics", 1998, 34 (3), pages 203-218; P.A. Thuermann, B.C. Hompesch, *Influence on Gender on the Pharmacokinetics and Pharmacodynamics of Drugs*,"International Journal of Clinical Pharmacology and Therapeutics", 1998, 36 (11), pages 586-590.

[18] Cf. A. Holdcroft, *Gender Bias in Research: How does it affect Evidence Based Medicine?*, editorial "J. Royal Soc. Med.", p. 100.

qualified workers); the change in the participation in the work-market (many traditionally male jobs are open to women), the strong female push towards a career, but the persistent difficulties in the work-market (the participation of women is nevertheless inferior to that of men, with greater unemployment problems or relinquishment of work places due to maternity and lack of working facilitations and social aids); the increase of the public participation on a social, political, economic basis, but the persistent marginalisation (there are still few women in positions of power and responsibility); the behavioural traits generally more frequent in women (e.g. the inclination to take care of others and the selflessness). The change of women's conditions from a historical, cultural and psychological point of view has relevant implications on their conditions of illness and health, on the way women perceive them and live through them. We highlight how, many pathologies traditionally attributed to the male gender because of their physical structure or their behavioural habits on an individual and social basis, are also widespread – and at times more greatly – in the female sex, due to the change in lifestyles and risk factors and/or to a lack of an adequate prevention, diagnosis and cure.

The research on women's health, elaborated by NOWH (National Observatory on Women's Health) in collaboration with the National Observatory of Health in Italian Regions, part of the Catholic University of the Sacred Heart[19], highlights (in the second part: "Health needs and health assistance") the condition of women's health and the quality of health assistance. In the pathologies most common in women – where the frequency of the pathologies is linked to age and social condition – we can find some relevant elements: an increase in cardiac pathologies (arterial hypertension, coronary cardiomyopathy, peripheral arteriopathy and cardiac imbalance, thromboembolic pathologies); an increment in the oncological field, as well as "female cancers" (breast cancer, carcinoma of the uterine cervix, endometrial tumours, ovarian neoplasia), also of trachea-bronchi-lungs tumours, due to the spread of nicotine addition even during adolescence; an increase in psychological pathologies (anxiety and depressive syndromes, eating disorders, psychotic syndromes); a tendency to an increase in obesity, due to the lack of physical activity and sedentary life, with an increase in the risk of cardiovascular illnesses and diabetes; an increase in alcohol abuse (with nutritional imbalances and dependency); an increase in neurodegenerative illnesses (Alzheimer's illness, Parkinson disease, multiple sclerosis, senile dementia); an increase in problems linked to infertility, caused by the postponement of the decision to have children or by the protracted use of contraceptives; problems and pathologies linked with the non-acceptance of aging also emerge[20].

These changes in the conditions of women's health and illness emphasise even more the lack of an adequately differentiated trails for the care of women's health, beyond traditional areas.

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[19] *La salute della donna. Stato di salute a assistenza nelle regioni italiane. Libro bianco,* Franco Angeli, Milano 2007.

[20] Different the causes: the problems of the substitutive hormonal therapy; the possibility to postpone for decades physical aging, extending the menstrual cycle for years as well as intervening with plastic surgery, with possible dangers for women's health, and not only because of the bad quality of the treatments – as in the case of deaths due to routing operations, like liposuction – but also because of extended negative effects, injected liquids and stress, due to the effort of not showing their real age.

5. *Women as drug users and the problem of the side-effects*

The fact that women are not adequately taken into consideration within clinical trails is penalising, given the increase in the consumption of drugs on their part.

As we can see from the data on territorial assistance in relation to the consumption and the gross public expense per capita for reimbursed drugs (class A) of the Italian National Health Service[21], women appear to be the greatest consumers of drugs, in particular within the ages of 15 and 54 (cf. tab. 5). The reasons of the difference in the consumption of drugs, with regard to gender, would require complex pharmacoepidemiological analysis: some hypothesis have been formulated, according to which women take better care of themselves in comparison to men, they have better awareness of their pathological condition, but also undergo a greater number of treatments due to their reproductive state and to the fact that they are more easily affected by chronic but non-lethal pathologies[22].

But if women, in greater quantities, use drugs that have not been adequately tested on them, the result is inevitably a higher frequency and seriousness of adverse reactions, often due to overdosing or polytherapies[23]. In 2007 the national Net of pharmacovigilance highlighted that spontaneous reports of adverse reactions in women constitute 57% of the total (cf. tab. 6). Examples of adverse reactions in women are: serious arrhythmia, cardiac imbalances and breaking of limbs due to drugs, even when commonly consumed[24]. In the United States some drugs have been withdrawn from the market because of the high number of side effects reported in women[25].

6. *Female vulnerability in clinical trails: women as "weak subjects"*

The lower number of women participating in experimental studies is due to a variety of reasons[26].

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[21] Cf. National Observatory on the use of drugs, *L'uso dei farmaci in Italia*, 2006.

[22] Arno Project, *Donne e farmaci. Rapporto 2003*, vol. VII, Ed. Centauro, Bologna 2004.

[23] International analysis report a frequency 1,7 times higher and they highlight the gravity, including even hospital admissions, of 59% of women. Cf. M. Pirmohamed, S. Meakin, C. Green, et. Al., *Adverse Drug Reactions as cause of Admission to Hospital: Prospective Analysis of 18.820 Patients*, "British Medical Journal", 2004, 329, pages 15-19.

[24] An example of this is aspirin, which is used by both men and women as prevention for cardiovascular pathologies. It induces adverse reactions in higher percentage in women, due to a difference in blood coagulation. Cf. *The Puzzle of Aspirin and Sex*, "New England Journal of Medicine", 2005, 352, pages 1366-1368. A case that caused the interest of public opinion is represented by the events linked to Digoxin; the analysis, mentioned in a prestigious, international journal, highlighted that the drug, when given to men, protected them from the risk of death, however it did not protect female patients. Cf. R. Short, *Fracture Risk is a Class Effect of Glitazones*, "British Medical Journal", 2007, 334, p. 551; S. Saif Rathore, M.P.H. Yongfei Wang, H.M. Krumholtz, *Sex-Based Differences in the Effect of Diagoxin for the Treatment of Heart Failure*, "NEJM", 2002, 347, pages. 1403-1411.

[25] Cf. *Withdrawn Drugs Posed Greater Health Risk for Women then Man, GAO says*, "American Journal of Health-System Pharmacy", March 15, 2001, 58 (6), pages 458-462; United States General Accounting Office, *Drug Safety: Most Drugs Withdrawn in Recent Years had Greater Health Risk for Women*, Washington D.C. 2001.

[26] D. Wrigt, N.J. Chew, *Women as Subjects in Clinical Research*, "Applied Clinical Trials", 1996, 5 (9), pages 44-54; E. Shuster, *For her Own Good: Protecting (and Neglecting) Women in Research*, "Cambridge Quarterly of Healthcare Ethics", 1996, 5, pages 346-361.

a) Social reasons. Some sociological studies highlight women's difficulties in becoming part of clinical studies due to the lack of time (mainly because of their role of carers within the family or, in the case of working women, due to their double obligation at home and at work) or due to their low income (because of the not yet adequate participation of women in the work-market and because of their lower wages). In part the reticence to participate is also due to the recruiters' lack of attention to the practical and psychological needs of women.
b) External environmental reasons. There are also other factors linked with lifestyle or exposure to substances that can interact with the experimental drugs. In external working environments, generally any substances present should be known; in less controlled working environments however, risky conditions can occur. Even lifestyle, which includes dietary habits or the use of natural remedies, exposes the patients to substances that can influence the clinical response to the pharmacological experimentation. Women are generally more inclined to use natural substances or home remedies consolidated in the cultural tradition of the family. Even if in clinical experimentation the treatment in the various experimental branches is the same, it is not always possible to keep under control lifestyle differences and external factors that can affect the experimentation in a different way for men and women.
c) Economic reasons. The pharmaceutical industry prefers not to invest in the experimentation on women due to the inevitable rise in costs. The enlistment should necessarily be multiplied: to stratify the data according to gender, men and women should be recruited, doubling or quadrupling the amount of enlistments, increasing time and cost, trails costs and insurance costs to cover eventual negative effects. Even the use of female and male animals in the pre-clinical phase increases the time and the cost of the research. As the authorisation for the introduction of the drug on the market does not require it, the pharmaceutical industry is not motivated to undertake such studies, as they are seen as economically disadvantageous. On the other hand public funding chooses typically female pathologies (like osteoporosis during the menopause), to be able to better tackle the health policies of a country where women live longer, overlooking those pathologies traditionally considered not typical of the female population.
d) Biological reasons. Women have always been considered "difficult" subjects for trials, due to their biological and physiological differences, but especially for their enzymatic and hormonal differences, due to the variations during childbearing and non-childbearing age (menstrual cycle, pregnancy, breast feeding, menopause) and to the possible consumption of contraceptives for contraceptive or therapeutic reasons (estrogens and progestin modify women's metabolism; the estrogens also affect the way genes work). This kind of variability does not allow the collection of "clean data" in mixed sex trials and lowers the statistical relevance of the experimentation. Even when there are women involved in the trial, it is not certain that the enlisted number can allow us to see significant events.

e) Possible pregnancy during childbearing age[27]. One of the reasons that have led the pharmaceutical industry to exclude women from trials is connected to the possibility that the trial of a new drug could damage the foetus[28] in case of pregnancy. There is also the possibility that the studied drug could have negative effects even after the end of the trial, months later. This explains why in general the pharmaceutical industry imposes the use of specific hormonal contraceptives[29] as condition for the participation in a research that can be considered "without risk" for the foetus.

7. *The exclusion/inclusion of women of childbearing age in trials protocols*

Regarding the problem of pharmacological experimentation on women of childbearing age, the literature presents a variety of positions: within those, we report the most spread ones.

Some affirm that the inclusion of women of childbearing age in the trails is ethically of the outmost importance, when balancing the possible damage to the foetus (considered not yet to have dignity in a strong sense) with the predictable direct benefits to women and in general to society[30]. From this point of view, the a priori exclusion of women of childbearing age from trails (to protect the possible foetus) results in injustice in the biomedical research, as women do not have the same opportunities as men with regards to the cure of certain illnesses. The particular physio-psychological and social conditions of women should not justify their exclusion, but, on the contrary, motivate a differentiated study in comparison to men. The expectation of the pharmaceutical industry that women should use hormonal contraceptives is also criticised as restrictive of women's freedom intended as self-determination.

Others maintain that where clinical trials, even only hypothetically and probably, poses a danger to the foetus' life and health (here the foetus is recognised as a subject

[27] U. Halbreich, S.W. Carson, *Drug Studies in Women of Childbearing Age: Ethical and Methodological Considerations*, "J. Clin. Pharmacol.", 1989, 9, pages 328-333.

[28] The risks of teratogenicity for the foetus are classified as follows by the Food and Drug Administration: "controlled study without risk" when the safety of the drug in all stages of pregnancy has been demonstrated; "remote but possible risk" when in the studies on animals an increase in foetal anomalies has not been demonstrated but the risk is possible; "no chance to exclude risk" when the risks have been demonstrated by teratogen effects in the studies on animals and there are few studies on humans; "positive evidence of risk" when the teratogen effect has been demonstrated; "contraindicated during pregnancy" when there is positive evidence, in both studies on animals and humans, of the risk for the foetus. Even the potential benefits for women are variable and oscillate from the therapy for deadly illnesses that cannot be cured in any other way (for instance, cancer cures) to the cure of non-deadly pathologies (take into account the cure of acne).

[29] We refer to the use of hormonal contraceptives, as with the use of barrier contraceptives (e.g. preservatives), even if they do not interact with the drugs, there is a percentage of risk of pregnancy. The need for the use of contraceptives is functional to the experimentation to protect the foetus as well as to guarantee the conditions of homogeneity.

[30] This is also the theory supported by the feminist circle. Cf. D.A. DeBruin, *Justice and the Inclusion of Women in Clinical Studies: an Argument for Further Reform*, "Kennedy of Institute of Ethics Journal", 1994, 3, pages 533-538; Id., *No Longer Patient. Feminist Ethics and Health Care*, Temple University Press, Philadelphia 1992, pages 158-175; V. Merton, *Ethical Obstacles to the Participation of Women in Biomedical Research*, in Wolf S.M. (ed.), *Feminism and Bioethics. Beyond Reproduction*, Oxford University Press, Oxford-New York 1996.

having dignity in the strong sense), it is ethically advisable to women of childbearing age to avoid participating in clinical studies, as the risk to the new life overrides the potential benefits to women. However, it is accepted that women could decide to be part of the trials for social reasons or for personal health needs. In such cases, however, the imposition by the pharmaceutical industry to use hormonal contraceptives is not considered morally acceptable as, even for those who support this point of view this imposition is seen as detrimental to the freedom and the responsibility of those who choose to be subjected to the trials. It is felt that the woman's explicit commitment to avoid pregnancy is sufficient, and that it is up to her to choose the methods of birth control which coincide with her lifestyle and values, including abstaining from sexual intercourse[31].

8. *Female presence in medical teams and in ethical committees*

An important aspect of protecting women during the trials is the participation of women not only as "object" of the trials (that is as individuals enlisted in the trials), but also as trials' "subject", in the sense of active subjects, present in the medical teams that plan and define the trials' development and present in the ethical committees that evaluate the trials protocols. The presence of women could contribute to a greater focus on the relevance of women's participation to the trials and could allow greater sensitivity with regards to female needs, from a psychological and social point of view.

There is no data regarding the presence of women in medical teams, however, it is possible to verify the presence of women in ethical Committees through an analysis of the committees' composition, as reported by the data of the Observatory on trials. Generally women's presence, although often linked to the nursing sector and to the representative of patients, is consistent, even if almost always inferior to that of men, and is strongly dependent on local circumstances.

9. *International bioethical guidelines*

In the '70s explicit instructions emerged, that made rules for the exclusion of women from clinical studies with the aim of protecting the health of the future child, as dramatic cases of foetal death and severe damage to the infants had occurred, due to indiscriminate trials[32]. In 1977 the Food and Drug Administration (FDA) in the *General Considerations for the Clinical Evaluation of Drugs* recommended the exclusion from experimentation of women of childbearing age, especially in phases I and II, as the data on teratogenicity was not known, with the exception of women with deadly pathologies;

[31] This is the position that refers to the inseparability of the uniting and the procreating dimension of the marital act. Cf. R. Minacori, D. Sacchini, A.G. Spagnolo, *Women of Childbearing Potential as Research Subjects in Clinical Trials: Ethical Issues*, in A.G. Spagnolo, G. Gambino (edited by), *Women's Health Issues*, Societa' Editrice Universo, Roma 2003, pages 123-129; A.G. Spagnolo, M. Cicerone, *Sperimantazione farmacologica e donne in eta' fertile*, "Medicina e Morale", from international literature, 2005, 3, pages 667-670; Catholic University of the Sacred Heart, ethical Committee, *Raccomandazioni riguardo alla inclusione di donne in eta' fertile nei protocolli di sperimentazione clinica*, "Medicina e Morale", 1996, 46, pages 141-143. Cf. for a historical reconstruction M. Pelaja, L. Scaraffia, *Due in una carne. Chiesa e sessualita' nella storia*, Laterza, Bari 2008, page 261 and following.

[32] S. Cagliano, *Dieci farmaci che sconvolsero il mondo*, Laterza, Rome-Bari 1994, pages 43-68.

women of childbearing age could participate to the studies in phases II and III only if sufficient information on the drug's safety and efficacy, even in the studies on animals, had been collected, which excluded interferences with the reproductive functions. In 1982 the World Health Organisation promulgated the *Proposed International Guidelines* which affirmed the duty to exclude women from non-therapeutic experimentations on healthy volunteers[33].

In 1988 we register a radical change in the direction of the FDA that, with the publication of the document *Guideline for the Format and Content of the Clinical and Statistical Sections of the New Drug Application*, highlights the under-representation of women in pharmacological trial and recommends the analysis of sex-differentiated data in clinical trials[34]. In 1993 the FDA again issued the *Guidelines for the Study and Evaluation of gender Differences in the Clinical Evaluation of Drugs*, recognising that the percentage of the participation of women to clinical experimentations in pathologies not typically female is inferior to that of men and hoping for the inclusion of women in the trials protocols with the aim to guarantee equal representation. The FDA accepts that such exclusion could have, in subtle ways, caused the impression that men are the "primary focus" of medicine and of pharmacological development, with women being of secondary consideration; it therefore recommends the removal of the prohibition of the participation of women of childbearing age to the first phases of trial, with the aim to prevent forms of discrimination, avoiding a paternalistic attitude. The FDA believes that it is not necessary to exclude women because of the potential risks to the foetus, as the risks can be minimised with an explicit commitment of the woman to avoid pregnancy, as well as through the use of laboratory tests which can ascertain such behaviours. The FDA does not impose any obligations on the pharmaceutical industry and to IRBs (Institutional Review Boards, equivalent to independent ethical Committees), to include women in experimentation, but it aims to remove the "not necessary impediment", in order to boost a higher participation of women in trials, leaving "flexibility" to the IRBs, to the researchers, to the sponsors and also, all considered, to the patients who have been correctly informed with regards to determining the safest measures to protect their health and individual rights, recognising the responsible autonomy of women as research subjects.

At an international level these issues are included in an indicative document within the medical field. Also in 1993 the Council for International Organizations of Medical Sciences (CIOMS) promulgates the *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (revised in 2002), recommending the researchers, the sponsors and the ethical committees to avoid excluding women of childbearing age from trials, as they do not believe the possibility of a pregnancy is sufficient reason to preclude or limit their participation and recognising that women have the ability to take a "rational decision" in participating in research (guideline number 16). In the case of risk to the foetus' health, women have to accept to undertake a pregnancy

[33] K.L. Baird, *The New NIH and FDA Medical Research Policies: Targeting Gender, Promoting Justice*, "Journal of Health Politics, Politics and Law", 1999, 24 (3), pages 531-566.

[34] R.B. Merkatz, *Historical Background of Changes in FDA Policy on the Study and Evaluation of Drugs in Women*, "Acad Med", 1994, 69, pages 703-707; R.B. Merkatz, R. Temple, S. Sobel, *Women in Clinical Trials of new Drugs. A Change in Food and Drug Administration Policy*, "The New England Journal of Medicine", 1993, 329 (4), pages 292-296.

test and to use an "effective contraceptive method", allowing, with such procedures, their enlistment also in the first phases of the trials with controlled doses of the new substance; we highlight that the informed consent must be guaranteed offering women a fair amount of time and adequate environmental conditions to decide, believing that an individual consent is a must, and that it cannot be substituted by the partner's consent. In addition, CIOMS recommends that even pregnant women are acceptable (guideline number 17) as trials subjects, provided that the risks (for the woman and for the foetus) are minimised, leaving the decision to the individual woman, even in the case of uncertainty and ambiguity about the definition of risk; the research can be promoted only if it is relevant to the health of the woman who is subjected to the trials and to other women in the same condition; it is believed that women can be recruited into the research only in case there are pre-clinical studies which state the drug's teratogenity.

In 1994 in the United States, a dedicated office called "Office of Women's Health" was created as part of the FDA, with the objective of boosting the inclusion of women in clinical studies, evaluating the different responses for the safety and the efficacy of drugs. In 1995 the previous instructions were strengthened further in the document *Investigational New Drug Applications*, which explicitly demands an end to any discrimination due to sexual difference, as well as age and race, in trials. In 1998 the FDA promulgates the *Final Rule on the Investigational Drug Applications* with the aim of actively intervening with sponsors who do not respect the instructions of fairness within sexual difference. In 1999 the working group "FDA-MA Women and Minorities Working Group" was created, with the aim of drawing up specific guidelines to boost the correct inclusion of women and of weak subjects in clinical trials. In 2001 the National Institute of Health in the USA issued the document *Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research* to promote a policy of women's inclusion in the enlistment for pharmacological trials. It is important to highlight that the Department of Health and Human Services in issuing the *Regulations for the Protection of Human Subjects* in 2001, does not take explicitely into account tendencies and directives for the researchers, the doctors and IRBs on the specific theme of trials on women of childbearing age.

Within the European biolegislation we highlight the focus on female specificity within the general area of health[35], but lacking specific provisions of policies of non-exclusion or inclusion of women in clinical studies (simply highlighting the lack of data in such field)[36]. There are however some initiatives of awareness. In 1998, the EMEA

[35] M.T. Ruiz Cantero, M.A. Pardo, *European Medicines Agency Policies for Clinical Trials Leave Women Unprotected*, "Journal Epidemiol. Community Health", 2006, 60, pages 911-913.

[36] The World Health Organization, Regional Office for Europe, specifically focused on the issue of the difference between sexes within Health System in general, without explicit reference to the issue of trial. Starting with highlighting the differences in social roles and in male and female behaviours, the WHO states that the health risk factors are inevitably different. For this reason it promoted the program "Gender and Health Program" with the aim of identifying the inequalities (the disadvantages of women in comparison to men) and of elaborating active responses to promote equality in the Health System with regards to the policies, the organisation of the services and the access to cures, adequate to the different needs determined by sexual difference. In 1999, in the document *Highlights on Women's Health in Europe*, the WHO lists Italy amongst the European countries lacking in the supplying specific data on female health in comparison to data on the population in general. Due to the position of the Committee of Ministers of the Council of Europe, in 1998 the Report *Mainstreaming: Conceptual Framework Methodology and Presentation of Good Practice* was elaborated by the Comité Directeur pour l'égalitée de gendre (CDEG),

(European Agency for the Evaluation of Pharmaceutical Products) issued the *Note for Guidance on General Considerations for Clinical Trials* allowing women of childbearing age to be part of clinical studies only if they were using contraceptives. Again the EMEA in 2003, after the contribution of a working group that included female researchers and representatives of the pharmaceutical industries from the whole of Europe (XX group), published the *Note for Guidance on the Clinical Development of HIV-Medical Products* recommending the elaboratation of study protocols which would promote the comparison between sexes, with the guarantee of a statistically significant participation of women and adequate medical training. In the document *Gender Considerations in the Conduct of Clinical Trials* issued by the Committee for Medical Products for Human Use (CHMP) of the European Drugs' Agency (EMEA) in January 2005, the lack of need for the elaboration of specific European guidelines on pharmacological trials on women is explicitely stated (differently to what occurred in reference to age difference, with regards to underage and elderly patients) considering as sufficient the international guidelines on the issue.

10. *National legislation*

In the Italian legal system there is no explicit reference to the female condition within clinical trials. In the legislative decree of the 24th of June 2003 number 211 *Carrying out of the directive 2001/20/CE in relation to the application of good clinical practice in the execution of clinical trials of drugs for clinical use* to the article 1 c. 2 "The respect of good practice guarantees the protection of the rights, safety and wellbeing of the subjects and ensures the credibility of the data regarding the same clinical trials", we refer to the "subject" intended as "person who participates to the clinical trials, both as the target for the experimented drug as well as its test" (art. 2. i.), without distinction between men and women. We speak of protection of the trials' subjects, with particular reference to adults unable to give their informed consent and to minors, but no explicit reference to women.

The new regulation on *Minimum requiremenst for the creation, the organisation and the functioning of ethical Committees for the trials of drugs* (ministerial decree of the 12th of May 2006) does not specify that there must be a balanced representation of both sexes.

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intergovernamental body responsible for the definition and the implementation of the actions of the Council of Europe that aim to promote equality between men and women. The Report was supposed to provide the conceptual basis, where the need to take into consideration sexual differences in the context of their differing social roles was highlighted, for any future action that would be recommended to all the States members of the Council of Europe. The European Health Committee (CDSP-European Council), starting with a careful evaluation of the current situation with regards to the theme "women and health" and with an insufficient analysis in the European countries, highlights the lack of detailed information about the access to cures by men and women, the necessity to pre-empt discriminations in order to also improve the efficacy of health policies from an economic point of view. In particular the Committee highlights the lack of sex-disaggregated data and of indicators to define the effects of the difference between men and women in health research; the need to implement health policies in the consideration of sexual differences. In conclusion the document refers to existing distorsions in biomedical research, with specific reference to pharmacological tests conducted exclusively on male subjects.

11. *Bioethical recommendations*

1. The NBC intends to highlight some elements of bioethical relevance for the promotion of women's health in those sectors of clinical experimentation that appear to suffer most from a kind of "neutralistic" ideology of medicine. In particular the NBC intends to underline the fundamental ethical principle of the fairness of a pharmacological trial on both men and women, in real conditions of equality, without exclusions or undue marginalisations, deeming necessary the identification and the removal of the causes of this unfairness. Just as a pharmacological trial that takes into account the conditions of fragility due to the patient's age (for example periatric and geriatric trials) must be deemed fair and right, in the same way a trial that takes adequately into consideration sexual differences must be deemed proper.
2. The NBC hopes for a boost, already at the level of biomedical research, of studies specifically directed at the analysis of the condition of women's health (diffused illnesses, risk factors, incidence, etc.), also and especially in the light of recent changes in their psychological-social and cultural condition, in order to identify the areas of deficiency of the health system in response to new and variable female needs. The study of physiological and psychological aspects should be implemented in this direction, as well as the analysis of social and cultural factors and their interaction with female health.
3. The NBC deems the increase of bioethically relevant clinical trials on women, as an important step towards guaranteeing the effective conditions of equality of care in comparison to men: the scarse representativeness of women and the lack of sex-differentiatied data constitute a discriminatory element for women's health. The increase in clinical trials must be promoted not just with regard to traditionally female pathologies but also for new pathologies, hoping for a link between the results of sex differentiated medical research and pharmacological trials. To this end, we recommend an increase of women's enlistment in clinical trials at every phase, even when studying the drugs' efficacy and their effect, promoting a sex differentiated analysis of the data. Trials should take into account sexual differences even at the pre-clinical level, in order to evaluate the toxicity of drugs in animal experimentation, but also in the research of alternative methodologies. The stratification of data according to sexual difference should also be boosted after the authorisation to market has been granted, in order to highlight the negative effects on women, which can contribute to an improvement in the planning of the course of the trials.
4. The NBC believes that drug's labels should indicate whether the drug has been specifically tested on women or not and that they should clarify and highlight any element that could generate a different response in men and women. The lack of such references presumes an improper assimilation of women to men, with possible negative effects on women but also on men.

   5. The NBC believes that the way to increase sex differentiated pharmacological trials can be indicated as follows: a) raise awareness in the local health authorities and motivate the pharmaceutical industry to support sex differentiated trials, even if not very lucrative, promoting research projects on the issue, showing its social importance in the achievement of a real equality between men and women in their

access to healthcare; b) promote the participation of women to clinical trials, giving adequate information (even through the media) on the negative consequences of the lack of differentiated trials and on the social importance of female trials, guaranteeing support and specific attention to women's psychological and practical needs; c) ensure a greater presence of women as experimenters and as members of ethical committees in order to achieve an active participation of women (not only as researchers, but also as representatives of patients' associations) to the elaboration of the procedures for the protocols and for the relevant informed consent; to promote greater attention from ethical committees to sexual difference in research protocols; d) boost health training which focuses on the female dimension within pharmacological trials, as well as within research and cure; e) increase international cooperation, as well as national and local, with the focus on the female condition within clinical trials, involving health authorities and the pharmaceutical industry.

6. The NBC believes that even the participation of women of childbearing age in pharmacological trials is ethically and socially important, provided that an adequate protection of the future child can be guaranteed. The NBC highlights the importance of a preliminary consultation about the intended trials, including adequate information, clear and in full, according to an objective, technical-scientific classification of the risks and benefits that the study involves for the patient, but that also taking into account the risks for the foetus in case of pregnancy[37]. We must also take into account that the exclusion of women of childbearing age from trials does not allow, in practice, to protect the foetus, as women could take the experimented drug (but not tested on them) on the market with similar risks in case of pregnancy and, to make it worse, without adequate protection. The NBC believes that the inclusion of women of childbearing age in pharmacological trials that poses risks to the foetus needs, unavoidably, the woman's clear statement of a conscious and responsible commitment to avoid intercourse that could lead to pregnancy. If it is not possible to exclude a risk to the foetus' life and health within the trials, but there are possible benefits to women in general and in particular in the cure of illnesses, the NBC believes that requesting the commitment to take contraceptives as a safety measure believed necessary by the study's sponsor – to avoid pregnancy, as the trials could be damaging to the foetus – can be included in the criteria to participate in the study.
   In addition, the NBC believes that it is important that the woman's husband or partner is also involved in the informative counselling, as the choices being made involve them as a couple.
   The trial of drugs that can make hormonal contraceptives ineffective is an open problem, so it is the fact that there might be interactions between the treatments being studied and the contraceptive methods being used: in this case the experimenters have to adequately inform the woman (and also her husband or partner) and recruit only on condition of a commitment, clearly expressed in the informed consent (given a fair

[37] The risks for the foetus and the benefits for the woman must be put in the balance, according to a gradation of ethical justification: the experimentation of drugs that do not present any risks to the foetus is considered as devoid of problems (for any purpose, both for therapeutic and non-therapeutic purposes, e.g. esthetic purposes); the experimentation that present a certain or uncertain risk to the life or health of the future child is considered ethically unacceptable, with the exception of drugs that can cure serious illnesses for the woman who undergoes the trial

amount of time for reflection), to avoid starting a pregnancy during the time of the trials and, in some cases, also for a certain time afterwards, a time to be defined according to the typology of the trials. The woman, on her part, must be available to carry out checks (pregnancy tests) that allow the experimenters to verify the conditions of safety to proceed. The informed consent and the committment to avoid procreation applies also to men who enter a trial protocol which presents the risk of damage to the foetus through their gametes.

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Table 1

Year	**Clinical Trials**
2000	55
2001	45
2002	62
2003	57
2004	51
2005	66
2006	76
Total	**412**

Clinical trials on women within all clinical trials – Observatory for clinical trials (data AIFA 01/01/2000 - 31/12/2006)

Table 2

Year	**Number of Clinical Trials**	**% Phase II**	**% Phase III**	**% Phase IV**	**% Bioeq / Biod**	**% Tot.**
2000	55	45,5	47,3	5,5	1,8	100,0
2001	45	42,2	55,6	2,2	0,0	100,0
2002	62	48,4	50,0	1,6	0,0	100,0
2003	57	45,6	52,6	1,8	0,0	100,0
2004	51	49,0	41,2	9,8	0,0	100,0
2005	66	50,0	42,4	6,1	1,5	100,0
2006	76	47,4	43,4	7,9	1,3	100,0
Total	**412**	**47,1**	**47,1**	**5,1**	**0,0**	**100,0**

In clinical trials on women, phase I trials are not present (dati AIFA 01/01/2000 - 31/12/2006)

Table 3

Therapeutic Area	**CE women**	**%**	**% Italy**
Oncology	258	62,6	28,1
Gynecology and obstetrics	73	17,7	1,7
Illnesses of the muscle-skeletal system	33	8,0	2,7
Endocrinology	11	2,7	5,8
Neurology	7	1,7	8,2
Genito-urinary system	6	1,5	1,6
Anaesthesiology	6	1,5	1,4
Immunology and infectious diseases	5	1,2	9,4
Nephrology/Urology	5	1,2	3,4
Dermatology/Plastic surgery	4	1,0	2,2
Cardiology/Vascular illnesses	1	0,0	11,1
Gastroenterology	1	0,0	7,0
Psychiatry/Psychology	1	0,0	2,8
Pharmacology/Toxicology	1	0,0	0,8
Total	**412**	**100,0**	**100,0**

Clinical trials on women for therapeutic field (AIFA data 01/01/2000 - 31/12/2006)

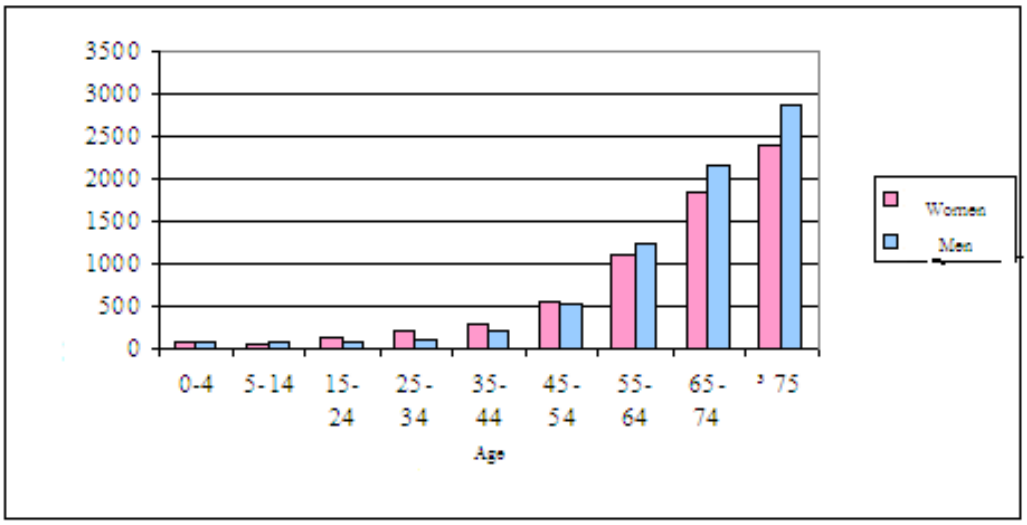
Table 4

Therapeutic class	Controlled clinical trials	N. subjects	Women (%)
Thrombolytics	176	279.179	24.1
Antithrombotics	103	167.878	27.0
Antiarrhythmics	80	45.430	22.6
Beta blockers	70	56.517	20.6
Antiaggregants	69	91.172	24.0

Data on the participation of women to clinical trial in the principal therapeutic classas (80% of trials). The table is part of a more extensive table: not all therapeutic classes have been referred to (the others cover 20% of the trials). In the original version RCT stands for 'Randomized Controlled Trials'. Data taken by P.Y. Lee, K.P. Alexander, B.G. Hammill et al., *Representation of Elderly Persons and Women in Published Randomized Trials of Acute Coronary Syndromes*, JAMA, 2001, 286(6), pages 708-713

Table 5

Territorial distribution of drug consumption
SSN by age and gender

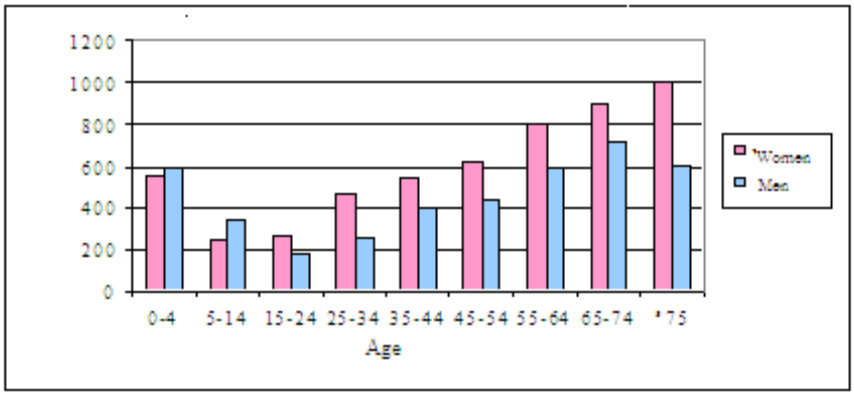


Source of data and year of reference: OsMed. Drug consumption in Italy. Year 2006

Drug consumption by age and sex (DDD – Defined Daily Dose per day per 1000 inhabitants)- AIFA (National Drug Agency) data regarding 2006.

Table 6

Adrs by gender and age



Source of data and year of reference:AIFA elaboration of the National Net of Pharmacovigilance. Year 2007.

Reported cases of adverse reactions to drugs (Adrs – Adverse Drug ReactionS) by sex and age – AIFA data regarding 2007.

Personal remark by Prof. Adriano Bompiani, Bruno Dallapiccola, Maria Luisa Di Pietro, Rodolfo Proietti

The "abstension" vote – and not a "contrary vote" – on the document "Pharmacological trials on women", approved by the National Bioethics Committee on the 28th of November 2008, is dictated by the awareness of the importance of a bioethical reflection on the question of the inclusion of women of childbearing age in pharmacological clinical trials. It is about – in this case – putting together important points for the progress of medical research and the marketing of new drugs, respecting the fundamental rights of the patients, if involved as trial subjects.

On the one hand we must, in fact, consider the need to include women in clinical trials in order to properly evaluate – in relation to the particular differences of the female organism – the pharmacokinetics, the pharmacodynamics, the toxicity, the efficacy and the safety of the new pharmacological treatments. This represents an unavoidable medical need, with regards to the therapeutic advantage that results from the evaluation of the therapeutic efficacy and of the side effects. In addition, the possibility to have access to a

clinical trial can constitute, especially for some situations of particular gravity (for example in the case of phatologies indifferent to standard treatments or of rare diseases) another opportunity of therapy – even if uncertain in outcome -, that can be *a priori* precluded to women because of their fertile condition. On the other hand, is equally important, for those who promote and conduct a clinical trial, to always consider the potential risk of teratogenicity in case of pregnancy, especially if there is already previous evidence from the studies on animals. From this, comes the absolute need, for potentially fertile subjects (even men carry such risk, when the drug can produce pathological changes of the spermatozoons), to avoid conception during the trial treatment and until the cessation of its effects.

We believe that these aspects have been well identified in the document and we agree with the arguments put forward in it.

We don't think, however, that it is ethically acceptable or justifiable from a medical point of view, to force the inclusion of potentially fertile patients in pharmacological clinical trials to use contraceptive methods chosen and imposed by the sponsor and supported by binding clauses from insurance companies, in order to give the necessary economical guarantees to cover possible damages. This request, independently from ethical and religious positions, is not in fact in keeping with the responsible freedom of choice that – within completely personal choices like those regarding married life and the responsibility to procreate – the patient applying to enlist in clinical trials must take on in a personal and independent way, after an exhaustive conversation with the doctor experimentator.

In addition, we highlight that contractual imposition from the sponsor of the trials to use contraceptive methods, gives ethical committees, which operate in health institutions regulated by particular rules, some evident difficulties in evaluating and accepting the protocols.