European Medicines Agency policies for clinical trials leave women unprotected

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in children's diet mean that their body fat levels (a trigger for puberty) are rapidly increasing and, elsewhere, general improvements in child nutrition and child health are yet to plateau. In all cases, public health measures can affect the age at which children enter physical puberty. Where this considerably precedes social puberty, resultant pressures on children will contribute to public health problems through naive approaches to sex, risk-taking and aggression. Instead of tackling the consequences of such naive behaviour, a better understanding of puberty at the population level may offer new opportunities to address risk factors. In the long term, public health strategies may attempt to retain the benefits of improved childhood nutrition and reduced infection without necessarily increasing the gap between physical and social puberty. In the short term, however, responding to earlier puberty means moving away from societal attitudes that equate protecting children with regarding them as firmly ensconced in childhood long after their physical journey into adulthood has begun. Such pretence, however well intentioned, simply denies them the vital information they require to complete this transition without damaging their health.

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Clinical trials

European Medicines Agency policies for clinical trials leave women unprotected

Maria Teresa Ruiz Cantero, Maria Angeles Pardo

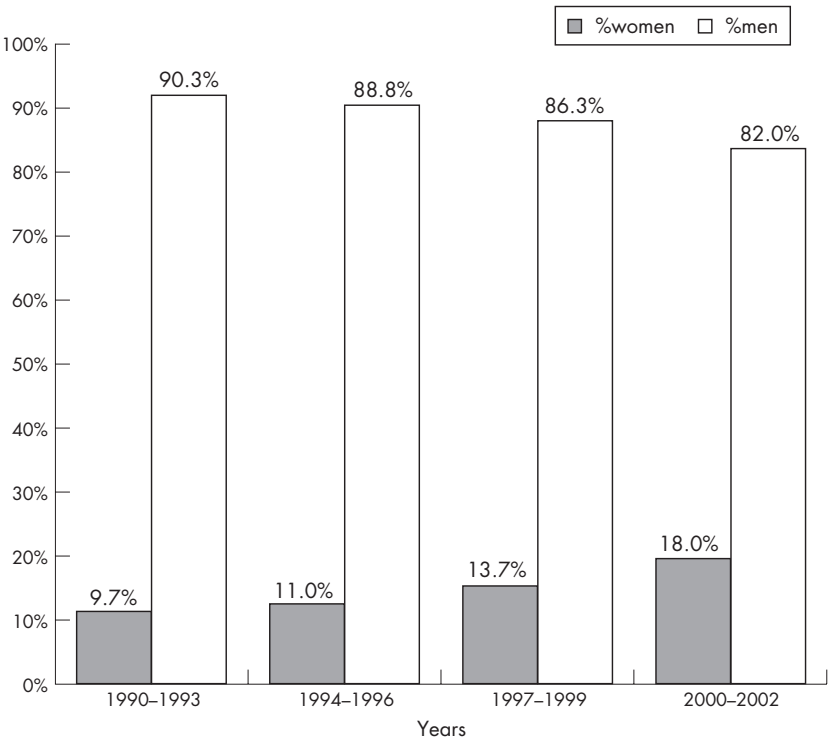
Relevance of equality of gender in clinical research

Specific strategies to implement guidelines for the study and evaluation of gender differences in the clinical evaluation of drugs have not been developed by the European Medicines Agency (EMEA). This agency accepts ''that some of the factors that influence the effect of a medicine in the population may be important when considering potential differences in response between men and women'' and ''gender-specific influences can also play a significant role in drug effect''. But besides these statements, in a document about gender considerations in the conduct of clinical trials, the EMEA argues against the need for separate International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines on women as a special population group, based on their internal review and experience, but without providing the sources.[1] The lack of sound fundaments of these convictions is worrisome. This paper analyses the document of EMEA,[1] and introduces some of the main reasons to reconsider the convenience to develop a policy on gender-related information for the clinical trials, an initiative already taken in the US.[2]

First of all, gender is not a demographic category of analysis as considered by the ICH guidelines. The parameters disaggregated by sex are not always the same as those by gender sensitivity (in some instances both are used as the same, but they are not equal). The information disaggregated by sex tells us whether differences by sex exist in some specific dimension of health, but the information by gender sensitivity is constructed to help to know the reasons (and consequences) of the sex differences. So, the term ''gender'' should be removed and replaced by ''sex'' in not all but many instances of the ICH guidelines.

As early as 1986, the NIH policy recommended for the inclusion of women in clinical research. In 1993, the NIH Revitalization Act required adequate numbers of women for valid analyses of differences related to phase 3 trials, and the Food and Drug Administration (FDA) guidelines ended the restriction on women of childbearing potential, emphasising sex representation in clinical trials to detect clinically significant differences.[3]

Clinical research in Europe was developed mostly in men until the 1990s. Afterwards, the ICH promoted the regulatory standards for clinical trials.[4] The ICH guideline E8 requires that the study population should be representative of the target patient population, and also demands phase I pharmacokinetic



N° patients	4409	16 409	11 404	9683
N° trials	9	32	33	43

Figure 1 Sex distribution in HIV clinical trials, 1990–2002.

information in women. Dose-response data need to be obtained for relevant subpopulations, ''according to gender'' as in Guideline E4. Guidelines E3 and M4E call for a characterisation of the patient population, analyses and critical assessment of the data with respect to sex. So, it appears that several of the ICH guidelines deal with gender issues today, although these recommendations are not reinforced as it is not usual that reports of clinical trials include the minimum gender information, such as

1. Sex distribution, which reflects the patient population, that will probably receive the treatment.
2. Subgroup analysis of men and women to permit meta-analyses.
3. Interaction analysis that permits the determination of differences between the sexes.
4. Gender-related content in discussion to state the limits to which the results can be generalised to the population outside the trial or to underline the differences in the responses of men and women.

The correct implementation of ICH guidelines permits the development of the above criteria, in a way identical to the FDA guidelines. But, the softness of the statements about the study samples for trials at the ICH guidelines, such as ''if the size of the study permits, important demographic or baseline value-defined subgroups should be examined……eg. comparison of effects by sex'', markedly weakens their recommendations.[1] This is mentioned in the ICH guidelines even when there is a prior hypothesis of a differential effect in a particular subgroup, with its assessment in the planning of statistical analysis.[4]

The facts showing that women were poorly represented in the samples of randomised controlled trials were published in *The New England Journal of Medicine*, *The Lancet*, *JAMA*, *Annals of Internal Medicine* and *BMJ*.[5]

Other published evidence shows that an appropriate subgroup analysis by sex is carried out only in a small part of the studies, and the design of trials does not allow the obtaining of gender-related information because the data are not adequately presented.[2 7] As a result of this created causation dilemma, the emphasis has changed from representation in clinical trials to analysis of subgroups within the broader analysis of safety and efficacy.

The case of treatments for HIV infection illustrates the variability in efficacy, toxicity profiles and pharmacokinetics by sex. However, clinical trials have been carried out with an insufficient number of women to allow carrying out sex-based analysis and detect sex differences. In a total of 117 randomised and controlled clinical trials of antiretroviral treatment efficacy in 41 905 adults, indexed in the Cochrane Controlled Trials Register (1990–2002), the proportional mean of women in the trials was 14.43% (fig 1). The percentage of women living with HIV/AIDS in 2002 in western Europe was 25% and overall in the world was 49%, so women included in trials are not representative of the population studied.[8] Only one trial provided data by sex. Only a 6% of the trials (7 trials) specified a stratified analysis by sex to determine differences. Only one of the 117 trials mentioned some gender-related information in the result and discussion sections.

Sex differences in pharmacokinetics and pharmacodynamics are widely recognised.[2 7 9] Although the EMEA accepts that women's participation in clinical trials is lower in the early phases of studies (phase I, and I–II), in which safety, safe dosage range and side effects are determined, the agency does not consider this inadequate representation to be relevant. As the appropriate doses and uses of drugs are generally established in the earlier phases of trials—in which dosing can examine the mechanisms by which women's response to drugs may differ from men's, including pharmacokinetics (bioavailability/absorption, distribution, metabolism and elimination), pharmacodynamics (pharmacological effect), hormonal interactions, binding with hormonal receptors, when women are excluded, any specific dosing requirements for them will remain undiscovered until much later in the drug development process, if ever. Fleisch *et al* reviewed the 2001 issues of three leading clinical pharmacology journals publishing early-phase drug trials; 239 studies, including 15 880 participants, were evaluated. Thirty one studies tested drugs with already published differences in pharmacokinetics and adverse reactions, and of them in only 9% (2/22) was a gender-specific analysis carried out, outlining the need for women's inclusion at those early phases.[6]

In a review of the clinical trials done with Vioxx (Rofecoxib), it was found from a gender analysis that more women (74%) than men were included in the trials.[10] But 80% of the trials did not describe efficacy results by sex, only one study reported side effects by sex and only 8% considered the influence of

hormonal variation in the results. The pharmacokinetic issues that related specifically to women were poorly followed: 60% of the trials did not specify the influence of oral contraceptives and in 88.9% the influence of oestrogen treatment was not included in the results. Pregnancy as exclusion criteria was only considered in only 50% of the trials. In this respect, it is noteworthy that 78% of the side effects reported to Vioxx in Spain occurred in women.

There should be a balance between the severity of the condition for which a drug is given and the severity of side effects accepted from its use.[9] Whereas a greater risk may be understood in drugs with essential therapeutic actions in severe conditions, in the case of non-steroidal anti-inflammatory drugs, which are used mostly to control symptoms of non-fatal diseases, the tolerance to severe side effects should be minimal.

The reason given for EMEA to lessen the relevance of not including enough women relates to the wide therapeutic index of most drugs essayed. This means that the variability between women and men that can affect the pharmacokinetics and pharmacodynamics of drugs is low and has no effect on the efficacy or security outcomes. However, there are several drugs that exhibit narrow therapeutic indexes (antipsychotics, warfarin, antiepilectics and immunosuppressive drugs).[12 13] So, small changes in dose or blood concentration can modify the efficacy or intensify the toxicity. Sex-based differences in the four major factors that contribute to interindividual pharmacokinetics variability have been identified. These differences have obvious relevance in the efficacy and side-effect profiles of various drugs in men and women. Overall, women have been reported to have a 1.5–1.7-fold greater risk than men of experiencing an adverse drug reaction.[14]

The US policy on drug safety has been debated in relation to the withdrawal of Rofecoxib (Vioxx). The FDA's counsel was accused of being close to the drug industry,[15] but this debate has rarely occurred in Europe.[16] Obstacles such as the increasing costs required to develop the larger sample sizes needed for sex-specific analyses, and the accelerated process to the approval of therapeutically novel drugs, hinder the progress in the European policy to implement the inclusion of women. However, to fulfil the gaps of knowledge and uncertainties related to sex differences in efficacy and safety in each phase of the trials, and essentially to avoid future problems, the EMEA should provide a regulatory clout to ensure safety and effectiveness for the women who use the drugs.

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APHORISM

''The conspiracy of silence in health care quality''

There is a conspiracy of silence about the quality of medical care and its hazards. This can only be addressed through professional action coupled with consumer action in a genuine partnership: the hammer and the anvil, or, as the South Africans say, ''one hand washes the other''. The implication of this is much more openness about results, outcomes, and failings and a willingness for professionals to be self-critical and for the public to be forgiving.

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