ICH INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

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SEX-RELATED CONSIDERATIONS IN THE CONDUCT OF CLINICAL TRIALS [1]

Preamble

This document has been updated to include reference to relevant new and revised ICH guidelines (Attachment A) and to reflect the recognized distinction between the concepts *sex* and *gender*.

Background

An underlying principle of drug development is that "patients entering clinical trials should be reasonably representative of the population that will be later treated by the drug"[2] as subpopulations may respond differently to a given drug treatment.

In recognition of this fact and the desire to facilitate the international development and optimal use of new medicines in the geriatric and pediatric populations, ICH has developed guidelines on the conduct of clinical trials in these two subgroups. This was considered of particular importance given the significance of age-related factors and, in the case of geriatrics, the possibility that concomitant medications could influence both the therapeutic and undesired actions of a new medicine.

It is known that some of the factors that influence the effect of a medicine in these populations may be important when considering potential differences in response between men and women. In addition, sex-specific influences can also play a significant role in drug effect.

While ICH has developed specific guidelines that deal with the participation of geriatric and pediatric subjects in the drug development process, this has not been the case for the clinical investigation of medicinal products in women. Direct and indirect references to sex and/or gender do, however, appear throughout a number of ICH guidelines[3].

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[1] While Considerations documents do not represent ICH guidelines, publication as an ICH document signifies the ICH Steering Committee's support for the principles, observations and conclusions contained therein. As appropriate, new or revised ICH guidelines should take account of this document regarding sex-related considerations in drug development, registration and subsequent use. Regional guidelines and legislation should also be consulted.

[2] ICH guideline E7: *Studies in Support of Special Populations: Geriatrics*.

[3] A situational review of ICH guidelines for relevant statements relating to subpopulations, demographics, gender, sex, etc. is appended to this report (Attachment A).

NOTE: The terms *sex* and *gender* have been used interchangeably in many of the previously adopted ICH guidelines. In recognition of currently accepted distinction between these concepts, the term *sex* will be used in all new and revised ICH guidelines to denote the biogenetic differences that distinguish males and females. While different definitions may exist respecting the term *gender*, it is understood that gender generally refers the array of socially constructed roles and relationships, behaviours and values that society ascribes to two sexes on a differentiated basis.

Reviews

In order to assess the need for a separate guideline on sex a review was undertaken of existing ICH guidelines and of regulatory experience in the three ICH regions, as determined from a study of new drug applications. Information on regional experience was primarily derived from the following sources[4]:

- USA: surveys conducted by the Food and Drug Administration (FDA) in 1983, 1989 and 2001 by the General Accounting Office (GAO) in 1992 and 2001;

- EU: a review by the European Medicines Agency (EMEA) of pivotal marketing application trials filed with the agency between 2000 and 2003, involving 84 products;

- Japan: a joint survey conducted by the Ministry of Health, Labour and Welfare (MHLW) and the Japanese Pharmaceutical Manufacturers Association (JPMA) involving all trials submitted for 60 new molecular entities (NMEs) approved between 2001 and 2003.

Observations

The principal findings from these reviews and current experience are as follows:

- ICH guidelines do address sex, in particular guidelines M4E and E3, which call for adequate demographic (including gender) characterization, analysis and assessment of the patient population. Other guidelines express the need to explore possible demographic (including sex) differences in dose-response (E4, M4E) and define certain safety precautions (E8, M3).

- In general, women are adequately represented in pivotal trial populations, typically reflecting the approximate extent one would predict from the gender prevalence of the disease or condition in the target population.

- Equally significant are results and experience which suggest that some form of evaluation for sex-related effect is generally conducted and expected, be it subpopulation analyses and/or pharmacokinetic (PK) / pharmacodynamic (PD) studies.[5]

While the term gender has been replaced by sex throughout this document, *gender (italicized)* has been retained when referring to existing ICH guidelines where this term appears. In all such cases, *gender* should be interpreted to read *sex*, as defined above.

[4] The results of US studies may be accessed via the FDA's Women's Health Initiatives web page at http://www.fda.gov/cder/audiences/women/default.htm. Results from the European and Japanese studies are to be published separately. A summary of studies is appended to this report (Attachment B).

[5] Refer to Attachment B for further details on regional experience.

- As anticipated, some deviations from expected results were observed but were mostly interpreted to be minor in nature. In assessing deviations, two factors should be considered: the difficulty in determining accurate estimates of disease prevalence in target populations and the variation in relative disease prevalence in the sexes with age; for example, the delayed onset of heart disease in women as compared to men.

- With respect to the inclusion of women of childbearing potential, the 1992 GAO survey revealed no significant difference in this subpopulation as compared to the overall population. The Japanese survey revealed that the percentage of women in Japanese trials involving subjects in the 16 -30 age bracket was lower (33%) than for other categories, but comparable in the 31- 45 age group (41%) to all other groups and to percentages seen in foreign trials.

- While women appear to be participating in all phases of study development, participation is lower in early (phase 1 – 1 / 2) studies.

Conclusion

The results of the above reviews and experience argue against the need for a separate ICH guideline on women as a special population in clinical trials. Relevant ICH and regional guidelines should be consulted for guidance on demographic considerations, including sex, in the design, conduct and analysis of clinical trials.

This issue may be revisited if future experience suggests a change from current practice.

ATTACHMENT A

REVIEW OF EXISTING ICH GUIDELINES

The following review summarizes some of the more relevant findings relating to the conduct, reporting and analysis of clinical trials and direct or indirect references to sex.

A number of ICH guidelines, in particular M4E (CTD - Efficacy) and E3 (Structure and Content of Clinical Study Reports), call for:

- a demographic **characterization of the patient population** so that possible differences in efficacy and safety can be identified. Critical variables will depend on the nature of the disease and the individual protocol, but would usually include demographic variables such as age, *sex*, etc. E3 also identifies menstrual status as a possible relevant factor. Where studies are sufficiently large, data should be presented according to these subgroups. At the summary level (Clinical Summary - Study Populations), the demographic characteristics of patients across all efficacy studies should be provided. Adverse events, extent of exposure and safety-related laboratory measurements and vital signs, etc. should include demographic data such as the age and *sex* of patients. An overview of demographic characteristics such be provided in the Summary of Clinical Safety.

- **analyses** of efficacy in specific populations, within a study if size permits and/or across multiple studies to evaluate effects of major demographic factors (Clinical Summary - Comparisons of results in subpopulations). Safety data, including more common adverse events, should be examined for relationships to factors including demographics such as age, *sex*, etc. All patient groups at increased risk should be identified.

- **critical assessments** of efficacy data (Clinical Overview) should describe the relevant features of patient populations, including demographic; similarity and differences in results in different subpopulations; observed relationships between efficacy, dose and dosage regimen in the different patient subgroups (E4); and efficacy in special populations. On the safety side, assessments should describe the nature of patient population/extent of exposure; limitations of the study database, including those related to study subject demographics; and differences in rates of adverse events in population subgroups, e.g., as defined by demographic factors. All of this information should be taken into consideration when determining the overall benefit/risk ratio and appropriate labeling for the product.

E4 (Dose-Response) states that **dose-response data** should be explored for possible differences in subsets based on demographic characteristics, such as age, *gender* or race. Differences should be described under Dosing recommendations - Clinical Summary (M4E). In this regard, both E4 and M4E refer to the conduct of PK studies to elucidate the influence of intrinsic factors. Of note: E8 (General Considerations for Clinical Trials) states that PK information in subpopulations, such as elderly children and *women* should be considered under the section on phase 1 trials.

E14 (QT Prolongation) notes that if the QT/QTc study is positive, analyses of ECG and adverse events from certain subgroups are of particular interest, such as female patients

Safety considerations: E8 and M3(R2) (Timing of Non-Clinical Studies in Relation to Clinical Studies) provide guidance on the inclusion of women in clinical trials, stating that:

- in general, pregnant women should be excluded from trials not intended for use in pregnancy . Where they are to be included, this decision should follow completion of all reproductive and genotoxicity studies, supplemented by available safety data from previous human exposure;

- women of childbearing potential should be using highly effective contraception. M3(R2) elaborates on requirements in the three ICH regions with regard to the nonclinical reproductive toxicity studies to be performed prior to the inclusion of this population in phase 1-3 studies. When hormonal contraceptives are being used, information on the potential effect of the product under study on the contraceptive should be addressed.

  M3(R2) further states that:

  - studies with the individual agent(s) of combination products that have shown findings indicative of embryo-fetal risk, combination studies are not recommended where the patient population includes women of child bearing potential;
  - women not of childbearing potential may be included in clinical trials without reproduction toxicity studies provided repeated dose toxicity studies (including evaluation of female reproductive organs) have been conducted. Examples of this population include permanently sterilized or postmenopausal women;
  - a male fertility study should be completed prior to the initiation of large scale or long duration clinical trials (e.g., phase 3)
  - in relation to clinical trials in the pediatric population, reproductive studies relevant to the age and *sex* of the pediatric population under study can provide important information on direct toxic or developmental risks.

  Furthermore, S5(R2) provides a consolidated strategy for testing medicinal products for their potential toxic effect on reproductive organs.

Discussion of demographics and sex in the E2 series of guidelines includes:

- the inclusion of *gender* as a data element for expedited reports;

- clarification of adverse event reporting rules for parent/child/fetus;

- a call, where possible, for an estimation of patient exposure , broken down by *sex* and age (E2C(R1) – Periodic Safety Update Reports and E2F - Development Safety Update Reports);

- in E2E (Prospective Pharmacovigilance Planning), the identification of pregnant women in relation to both the safety implications of populations not studied in the pre-approval phase and their inclusion in various pharmacovigilance methods; the stratification and discussion of important adverse events, wherever possible, by age, *gender* and ethnic origin; and recommendation to include demographics in

questionnaires as part of active surveillance methods.

ATTACHMENT B

REGIONAL EXPERIENCE

USA

The extent of participation of women in New Drug Application (NDA) trials filed with the FDA has been examined several times, by the FDA in 1983, 1989 and 2001 and by the General Accounting Office (GAO) in 1992 and 2001.

The 1983 survey, carried out primarily to assess the inclusion of the elderly, looked at representation by age and sex in 11 NDAs on hand at the FDA. In contrast, the 1989 survey targeted all drugs approved in 1988 in an effort to avoid possible selection bias. The survey, completed by industry, excluded phase 1 subjects/patients. In the end 12 of 20 approved drugs were examined. The 1992 GAO survey analyzed the sex, age, and race distribution of all NDAs approved between January 1988 and June 1991. Sponsors were requested to complete a questionnaire that included a breakout by age category. The age distribution allowed a separate analysis of women of childbearing potential, taken to be 15-49.

The results of the surveys indicated that, in general, males and females were represented in proportion to the prevalence of the disease or condition. The 1992 GAO survey also suggested that there was no significant difference in the percentage of women of childbearing potential as compared to the overall population.

While these studies were reassuring with respect to Male/Female representation, analyses of collected data for potential gender-related effects were not consistently being conducted at the time. This changed, however, with the introduction of the 1993 *Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs* and subsequent rules, with the result that analysis of safety and effectiveness data by sex is now expected and seen in US applications, as confirmed by the subsequent GAO and FDA reports.

The 2001 GAO report, commissioned to assess progress seen since the 1992 survey, examined application summaries and FDA medical review reports for 36 qualifying (sex neutral) NDAs submitted and deemed approvable between August 1998 and December 2000. The report concluded that women made up more than one-half the participants in small efficacy (phase 2) and pivotal (phase 3) studies, and that the majority of NDAs contained sex-related analyses of safety and efficacy. The report further notes that over 75 percent of NDAs reviewed had evidence of analysis of PK data for sex differences.

The 2001 FDA study involved a review of FDA medical officer reports and approved labeling for 185 NMEs, representing 2581 clinical trial protocols, approved by the Center for Drug Evaluation and Research (CDER) between January 1995 and December 1999. Report results and conclusions are congruent with those of the GAO report.

The FDA study also found that the majority of product labelling contains references to the evaluation of sex-related effects. When observed, most sex-related effects were pharmacokinetic in nature. Few products demonstrated safety or efficacy effects, and none recommended changes in dosage based on sex-related effects. Again, this is consistent with observations from the GAO review.

While women appear to be participating in all phases of study development, both reports also note the smaller proportion of women in phase 1 - 1 / 2 studies (approximately 15-30 percent for trials where this parameter could be evaluated).

EU

The EMEA has undertaken a review of pivotal marketing application trials for evidence of sex bias. [6] [7] The review, which involved marketing applications filed with agency between 2000 and 2003, was meant to assess whether the percentage of females in such trial populations is comparable to the target population. Ten randomly selected products have also been examined to assess whether the sponsor performed subgroup analyses by sex.

Data from 240 pivotal clinical trials involving 84 products have been assessed. An additional 27 products were excluded as candidates, among them products meant to treat conditions specific to one sex.

The review indicates that the percentage of females in study populations generally represents the expected percentage of females in the target populations. As expected, a high degree of variability was noted. Considerable variability was also sometimes seen within indications. The percentage of women was, as expected, lower in several indications and higher in others. While deviations were interpreted to be minor in nature, the report recommends that the apparent under representation of women in certain therapeutic categories (e.g. hypertension) and over representation in others (e.g. allergy) warrants further assessment. At the same time, the review also notes the inherent difficulties in obtaining accurate estimates of the expected percentage of females in the target population.

Findings from the randomized sample assessment reveal that some form of evaluation for sex-related effect was conducted in 8 of the 10 products, with Male/Female subgroup analysis for four products and PK/PD studies for an additional four. The study also notes that in two cases, subgroup analysis was probably not reasonable, owing to the size of individual trials and, additionally, the heterogeneity of clinical indications for one product.

Japan

The MHLW, in collaboration with the JPMA, has collected data on the participation of women in marketing application trials based on 60 new molecular entities (NMEs) approved between 2001 and 2003. Through the use of a questionnaire, information was collected on the total number of men and women in the overall clinical package (including phase 1 trials) and on the stratification by therapeutic field, age, phase of clinical development and the origin of clinical evidence (i.e., Japanese versus foreign trials).

Results from data collected indicate the following:

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[6] Pivotal trials are the main studies used in the benefit/risk assessment.

[7] Müllner M, Vamvakas S, Rietschel M, van Zwieten-Boot BJ.: Are women appropriately represented and assessed in clinical trials submitted for marketing authorization? A review of the database of the European Medicines Agency.Int J Clin Pharmacol Ther. 2007 Sep;45(9):477-84. The EMEA study notes that such trials usually involve two large randomized, controlled (phase 3) studies, but that under certain circumstances one phase 3 or even phase 2 studies may suffice for marketing authorization.

- Women represented 58 % of the total study population (involving 56 NMEs), including trials for 10 NMEs that are predominantly for use in women.[8] In the case of 44 NMEs with sex neutral indications, women constituted 42% of the overall trial population, a figure that was essentially the same for Japanese and for foreign conducted trials;

- In the case of sex neutral NMEs, women accounted for 44% of the subjects in phase 2 trials and 45% in phase 3 trials conducted in Japan, slightly higher than for foreign-run trials. However, results indicate that the participation of women in phase 1 - ½ studies is significantly higher in foreign trials (31%) than in Japanese trials (4%) due to the historical implementation of related guidelines;

- In the case of sex neutral NMEs, the percentage of women in the 16-30 age bracket in Japanese trials was lower (33%) than for other categories, but comparable in the 31-45 age group (41%) to all other groups (42% - 46%) and to percentages seen across age groups in foreign trials (42% - 49%).

The study authors conclude that while the number of female subjects in trials involving gender neutral NMEs was somewhat lower than for men, the difference was not significantly large to prevent appropriate evaluation of sex-related effect, if any. The report also notes the rise in the use of foreign data since the implementation of the ICH-E5 guideline, with pivotal foreign trials now submitted in addition to Japanese trials in a significant proportion of recent new drug applications.

[8] 10 NMEs were for predominately female diseases such as breast cancer, Sjogren's disease, osteoporosis and migraine.