



THERAPEUTIC PRODUCTS PROGRAMME GUIDELINES

INCLUSION OF WOMEN IN CLINICAL TRIALS

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Note (November 1997): This guideline has been revised to reflect Health Canada's Glossary of Definitions. The changes reflect the appropriate use of the words 'gender' and 'sex', with the latter referring to the biological differences which are of interest during the review of drug efficacy and safety. No other changes have been made to this document since its last issuance.

STATEMENT OF PURPOSE

It is important to ensure that women are enrolled in clinical trials at all stages of drug development in order to define the risks and benefits associated with drug therapy in this segment of the population. Since physiological changes and hormonal levels during child-bearing years and menopause, as well as the use of oral contraceptives or hormone replacement therapy, may affect the efficacy and safety of a drug, the influence of these parameters should be studied during drug development.

GENERAL PRINCIPLE

Drugs should be studied prior to approval in subjects representing the full range of patients likely to receive the drug once it is marketed. Although in most cases, drugs behave in a qualitatively similar manner in demographic (sex, age, race) and other (concomitant illness, concomitant drugs) subsets of the population, there are many quantitative differences, for example, in dose-response, maximum size of effect, or in the risk of an adverse event. Optimal use of drugs requires identification of these factors so that appropriate adjustments in dose, concomitant therapy and monitoring can be made.

The intention of this guideline is to encourage the inclusion of women, especially those of child-bearing potential at the earliest stages of drug development, in order (i) to ensure that potential sex-related differences are being identified and taken into consideration when planning Phase III pivotal trials and (ii) to generate appropriate data to inform both physicians and potential users concerning sex-related characteristics of a new drug.

While the Therapeutic Products Directorate is committed to a policy of enrolling women in the earliest stages of drug development, this does not reflect a lack of concern for potential fetal exposure or indifference to potential fetal damage. Rather, it is the opinion of the Therapeutic Products Directorate that exclusion of women from early trials is not necessary because in accordance with good medical practice, appropriate precautions against becoming pregnant and exposing a fetus to a potentially dangerous agent during the course of a study will be taken by women participating in clinical trials. It is also expected that women will receive adequate counseling about the importance of such precautions prior to entry into the trial. Furthermore, determinations about whether that risk is adequately addressed are properly left to patients, physicians, Ethics Review Boards, and sponsors, with appropriate review and guidance by the Therapeutic Products Directorate, as are all other aspects of the safety of proposed clinical trials.

SCOPE OF THE GUIDELINE

This guideline is directed principally toward new active substances (including biological products and radio pharmaceuticals), as well as new uses, new formulations, or combinations of approved drugs that are likely to be used by women.

DEFINITION OF THE POPULATION

The population of concern in this guideline includes women of child-bearing potential and post-menopausal women.

A decision to enrol pregnant or lactating women in a specific trial must be individualised and based on a careful risk/benefit assessment taking into consideration the nature and severity of the disease, the availability and results of preclinical animal data, the availability and risks associated with alternative therapy, the stage of pregnancy and the potential for harm to the fetus or infant.

CLINICAL EXPERIENCE

The guideline proposes the inclusion of women in clinical trials from the earliest stages of drug development.

Inclusion of Both Sexes in Clinical Trials

Patients of both sexes should be included in the same trials in numbers adequate to allow detection of clinically significant sex-related differences in drug response. In some cases, however, it may be appropriate to conduct studies in a single sex (e.g., to evaluate the effects of phases of the menstrual cycle on drug response).

Although it may be reasonable to exclude certain patients at early stages because of characteristics that might make evaluation of therapy more difficult (e.g., patients on concomitant therapy), such exclusion should usually be abandoned as soon as possible in later development so that drug-drug and drug-disease interactions can be detected. Thus, for example, there is ordinarily no good reason to exclude women using oral contraceptives or estrogen replacement therapy from clinical trials. Rather they should be included and differences in response between them and patients not on such therapy examined.

Precautions in Clinical Trials Including Women of Childbearing Potential

In accordance with good medical practice, clinical protocols should include measures that will minimize the possibility of fetal exposure to the investigational drug. These would ordinarily include providing for the use of a reliable method of contraception (or abstinence) for the duration of drug exposure (which may exceed the length of the study), and use of pregnancy testing prior to initiation of study treatment and at predetermined intervals during treatment, depending on the length of the study.

Further, it is expected that appropriate precautions against becoming pregnant and exposing a fetus to a potentially toxic agent during the course of the study will be taken by women participating in clinical trials. It is also expected that women will receive adequate counselling about the importance of utilizing a reliable method of contraception and will

be fully informed about the current state of animal reproductive studies and any other information about the teratogenic potential of the drug. This is essential when there exists a possibility that the new drug product may lessen the effectiveness of a hormonal contraceptive agent. In this case, patients should be advised to use a supplementary, non-hormonal method of contraception for the duration of the drug exposure.

In all cases, the Informed Consent document and the Investigator's Brochure should include all available information regarding the potential risk of fetal toxicity. If animal reproductive toxicity studies are complete, the results should be presented with some explanation of their significance in humans. If these studies have not been completed other pertinent information should be provided, such as a general assessment of fetal toxicity in drugs with related structures or pharmacologic effects. If no relevant information is available, the informed consent should explicitly note the potential for fetal risk.

In general, it is expected that reproductive toxicity studies will be completed before women of childbearing potential are enrolled in large scale and/or long-term Phase II and III studies during which significant drug exposure may occur.

Potential Effects on Fertility

Where abnormalities of reproductive organs or their function (spermatogenesis or ovulation) have been observed in experimental animals, the decision to include patients of reproductive age in a clinical study should be based on a careful risk-benefit evaluation, taking into account the nature of the abnormalities, the dosage needed to induce them, the consistency of the findings in different species, the severity of the illness being treated, the potential importance of the drug, the availability of alternative therapy, and the duration of therapy. Where patients of reproductive potential (this should apply to both sexes) are included in studies of drugs showing reproductive toxicity in animals, the clinical studies should include appropriate counseling on the utilization of reliable methods of contraception, monitoring, and/or laboratory studies to allow detection of these effects. Long-term follow-up will usually be needed to evaluate the effects of such drugs in humans. Patients should be made aware of the findings in animals, and the need for long-term follow-up, prior to study entry.

Pharmacokinetic Studies to Define Sex Differences

The pharmacokinetics of a drug should be defined for both sexes using either a specific pharmacokinetic study or a pharmacokinetic screen.

The following three pharmacokinetic issues related specifically to women that should be considered during drug development are:

- i) The influence of the menstrual cycle on the drug's pharmacokinetics, including both comparisons of premenopausal and postmenopausal patients and examination of within cycle changes.

ii) The influence of concomitant supplementary estrogen treatment or systemic contraceptives (oral contraceptives, long-acting progestin) on the drug's pharmacokinetics.

iii) The influence of the drug on the pharmacokinetics of oral contraceptives.

Which of these influences should be studied in a given case would depend on the drug's excretion, metabolism, and other pharmacokinetic properties, and on the steepness of the dose-response curve.

If there are pharmacokinetic differences between males and females, the influence of sex on drug-drug interactions should also be assessed.

Hormonal status during the menstrual cycle may affect plasma volume and the volume of distribution (and thus clearance) of drugs. The activity of certain cytochrome P450 enzymes may be influenced by estrogen levels and, in addition, microsomal oxidation by these enzymes may decline in the elderly more in men than women. Oral contraceptives can cause decreased clearance of drugs (e.g., imipramine, diazepam, chlordiazepoxide, phenytoin, caffeine, and cyclosporine), apparently by inhibiting hepatic metabolism. They can also increase clearance by inducing drug metabolism (e.g., of acetaminophen, salicylic acid, morphine, lorazepam, temazepam, oxazepam, and clofibrate). Certain anticonvulsants (carbamazepine, phenytoin) and antibiotics (rifampin) can reduce the effectiveness of oral contraceptives. Many of the potential interactions of sex and sex-related characteristics (e.g., use of oral contraceptives) can be evaluated with the pharmacokinetic screen. In some cases, specific studies will be needed.

Analysis of Efficacy and Safety by Sex

Analyses to detect the influence of sex should be carried out both for individual studies and in the overall integrated analysis of efficacy and safety. Such analyses of subsets can be expected to detect only relatively large differences, but in general, small differences are less likely to be clinically relevant.