GUIDANCE DOCUMENT

Considerations for Inclusion of Women in Clinical Trials and Analysis of Sex Differences
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Health Products and Food Branch
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FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on how to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidance documents.

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1. INTRODUCTION

1.1. Policy objective

This document provides guidance on the study and analysis of sex differences in clinical trials of therapeutic products in order to generate evidence to advise on the optimal use of therapeutic products in both women and men. For many years, it was accepted that women did not differ from men except where their reproductive organs were concerned. Thus it was assumed that, data obtained from research involving male subjects could simply be extrapolated to women, and therefore, there was no need to include female subjects in studies (clinical trials). However, scientific evidence shows that there are often many clinically meaningful differences. As such, this guidance addresses considerations pertaining to the appropriate inclusion of women in all stages of clinical trials and research with the aim of identifying and analyzing sex-related differences that may affect the safety and efficacy of a therapeutic product.

This guidance document reflects the Government of Canada’s Health Portfolio Sex and Gender-based Analysis (SGBA) Policy which supports the development of sound science and the implementation of rigorous and effective research that expands the understanding of health determinants in both sexes in order to provide knowledge which can result in improvements in health and health care. While this guidance recognizes the importance of the elements of a diversity framework, such as ethnicity, socioeconomic status, disability, sexual orientation, migration status, age and physical status (early menopause etc.), it focuses on sex-related differences in clinical trials.


1.2. Principles

This guideline supports the conduct of studies in accordance with generally accepted Good Clinical Practices (GCPs) that are designed to ensure the protection of the rights, safety and well-being of clinical trial subjects. This includes the GCPs referred to in Division 5, Part C of the Food and Drug Regulations, Part 4 of the Natural Health Products Regulations, and described in the International Conference on Harmonisation (ICH) Guidance (E6) on Good Clinical Practice and in ISO14155, Clinical Investigation of Medical Devices for Human Subjects.

This Guidance is also consistent with the International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002) of the Council for International Organizations of Medical Sciences (CIOMS) and with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (2010) where it states that “Women shall not be inappropriately excluded from research solely on the basis of gender or sex” (Article 4.2).

1.3. Policy statements

1 Government of Canada’s Health Portfolio, Sex and Gender Based Analysis Policy, 2009
2 Sex refers to the biological characteristics such as anatomy (e.g. body size and shape) and physiology (e.g. hormonal activity or functioning of organs) that distinguish males and females (SGBA Policy, 2009).
Prior to receiving market authorization in Canada, therapeutic products should be evaluated in subjects who are representative of the full range of persons likely to receive the product.

In general, clinical trials should enrol subjects representative of the population(s) expected to use the therapeutic product. Specifically:

- It is recommended that a representative number of women be included in clinical trials for therapeutic products that are intended to be used specifically by women or by heterogeneous populations that include women.

- It is recommended that women, including those of child-bearing potential and postmenopausal women, be included at the earliest possible stages of clinical trial research so that potential sex-related differences are identified and taken into consideration when planning Phase III pivotal trials.

- Although it may be reasonable to exclude certain potential subjects at early stages due to characteristics that may render evaluation of therapy more difficult (e.g. women and/or men on concomitant therapies), inclusion of such subjects is encouraged as early as possible in phases of clinical development so that therapeutic product interactions (e.g. drug-drug; natural health product-drug; natural health product- natural health product and product-disease) can be identified and assessed.

1.4. Scope and application

This guidance applies to sponsors, who conduct research for therapeutic products that include, but may not be limited to, the following: Pharmaceuticals, biologics, genetic therapies, radiopharmaceuticals, natural health products and medical devices, including new active substances and new formulations, new uses/indications and combinations of therapeutic products.

This guidance applies primarily to clinical trial research. However, the development of a therapeutic product is a stepwise process involving development of both animal and human efficacy and safety information. Therefore, this guidance also addresses nonclinical research as the foundation for the conduct of human clinical trials. Where relevant, it also notes other considerations pertinent to the life-cycle of a therapeutic product.

This guidance addresses considerations regarding women of all ages, including women of child-bearing potential and women who are not of child-bearing potential (see definitions, Appendix 3).}

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3 Representative of the full range of persons include men and women of all ages including women of child-bearing potential, women who are not of child-bearing potential, pregnant and breastfeeding women at the outset.

4 “A representative number of women” means that the number/percentage of women needs to be in proportion to the prevalence of disease treated in women. The selected population of women should be diverse, including women of various age groups and ethnicities.

5 Sponsors should consult the ICH Guidance M3 (R2) regarding the inclusion of pregnant women in early stages of clinical trials.
A), as subjects in clinical trial research. Some of the issues addressed in this guidance may also be pertinent to adolescent girls (12 up to 18 years of age) who are subjects in clinical trial research.

In addition, this guidance:

- Addresses considerations pertaining to pregnant or breastfeeding women and to sexual partners of clinical trial subjects. It is structured to provide separate recommendations for clinical trials that include non-pregnant women (informed consent; pregnancy prevention/contraception; inadvertent pregnancy) as well as clinical trials that include pregnant and breastfeeding women.

In this guidance document, “shall” is used to express a requirement, i.e., a provision that the user is obliged to satisfy in order to comply with the regulatory requirements; “should” is used to express a recommendation which is advised but not required; and “may” is used to express an option which is permissible within the limits of the guidance document.

1.5. Background


The Guidance Document on the Inclusion of Women in Clinical Trials was released in 1997 to support inclusion of women in all phases of clinical trials research and provide guidance to sponsors on how to implement the policy objective. Since the 1990s, evidence suggests there has been increased inclusion of women, particularly in Phase III clinical trials. As well, regulators now expect that nonclinical and pharmacokinetic studies are carried out, as appropriate to the product, to identify potential sex differences in the development of a therapeutic product. However, women are still underrepresented in early phase trials, and in trials for some therapeutic areas such as cardiovascular disease. As well pregnant and breastfeeding women are generally excluded from clinical trials. As a result, there is limited information to advise the use of therapeutic products by these women, despite widespread use of therapeutic products in pregnancy and while breastfeeding.

Over the past several decades, scientific knowledge has increased about sex differences in risk factors, symptoms, pathways, and about the outcomes of interventions for particular diseases and conditions. There are known sex differences in how women and men absorb, metabolize and excrete certain therapeutic products (e.g. antidepressants and antipsychotics, antibiotics and antiarrhythmics). It is theorized that these pharmacokinetic differences stem from variations between the sexes due to factors such as body weight, plasma volume, gastric emptying time, plasma protein levels, metabolizing enzymes, drug transporter function and clearance activity. Sex differences in pharmacodynamics have been observed in drugs acting on the central nervous system, immune system, cardiovascular system and on energy metabolism. Also, evidence suggests that being female is a risk factor for the development of adverse drug reactions, and that
the prevalence and nature (severity) of adverse events may differ between men and women, depending on the product type and condition treated.

Similarly, there is evidence of sex-related differences in the use of, and in response to, some medical devices. For example, response to cardiovascular devices may be influenced by the later age at which women tend to develop heart disease, women’s smaller heart structure or physiological differences. Responses to musculoskeletal implants reflect anatomical differences by sex, and some *in vitro diagnostic devices* are sex specific but most may be used for both males and females. Also, there are selected analytes (e.g. certain cardiac markers) where ranges for normal and disease states are sex dependent.

Despite known differences, there is currently limited reporting of sex and/or gender related differences in the published results of clinical trial research. There is also some evidence to indicate that data analysis by sex is not carried out consistently for therapeutic products.

Women constitute a large portion of the consumers of therapeutic products, including prescription drugs, medical devices and natural health products. Some of these products are used for conditions unique to women’s physiology (e.g. menstruation, menopause, and pregnancy), others for conditions that have greater prevalence in women (e.g. autoimmune diseases; osteoporosis) and others for conditions that tend to affect both women and men equally.

Accordingly, Health Canada encourages sponsors to collect and document information concerning differences between sexes in response to therapeutic products and regarding therapeutic products used in pregnancy and while breastfeeding. Increased information on the safety and efficacy of products used in pregnancy, or while breastfeeding, can inform health care decisions.

Analysis of clinical trial data by sex may identify clinically relevant sex differences in therapeutic response and, as a result, minimize the risks, maximize benefits and promote the optimal use of therapeutic products in both women and men.

**This updated Health Canada guidance document supersedes the 1997 Guidance Document on the Inclusion of Women in Clinical Trials and has been developed to:**

- Clarify the scope of the original guidance, including the populations to which it applies;
- Provide further guidance to sponsors on issues not addressed or minimally addressed in the 1997 guidance document. These include: inadvertent pregnancy during the course of a clinical trial and inclusion of pregnant and breastfeeding women in clinical trials;
- Support and encourage good therapeutic product development practices, including new approaches and methodologies, to identify and analyze potential sex differences across the product life cycle;
- Provide guidance within the current regulatory environment.

This guideline encourages the generation and consideration of new scientific knowledge about sex differences, and about therapeutic products used in pregnancy and/or while breastfeeding. It also recognizes the importance of building the evidence base not only throughout the clinical
trial process, but also throughout the product lifecycle from non-clinical studies through to post-market surveillance.

2. GUIDANCE FOR IMPLEMENTATION

Where sponsors intend a therapeutic product to be used by both women and men, it is recommended that sponsors include both sexes in: (a) nonclinical studies; and: (b) in clinical trials to allow detection of potential sex-related differences in efficacy and in safety.

In some instances, further confirmatory studies in a single sex may be appropriate, in particular when a product is intended for use in one sex exclusively. Evaluation of the effects of phases of the menstrual cycle on therapeutic product response in females should also be considered.

2.1. Nonclinical studies

Nonclinical studies conducted in both male and female animals to determine pharmacokinetics, pharmacodynamics, pharmacology and toxicology can suggest potential sex-related differences in concentration response, safety and/or efficacy. The results of such studies may provide signals for potential sex-related differences in humans to be further explored in human studies. Nonclinical studies may provide early signals of the teratogenic potential of products under development. Such information is an important consideration for the informed consent process for human studies, particularly where women of childbearing potential or pregnant women may be exposed to the product. (See also Section 2.3).

Nonclinical studies should be undertaken according to requirements specific to the product or product class. Requirements may differ between pharmaceuticals, biologics and natural health products. Biologics, including vaccines, have unique and diverse structural and biological properties for which there are particular considerations of species specificity, immunogenicity and where the actions of the product may be pleiotropic. Sponsors should refer to the relevant ICH Guidance documents and other relevant international guidances, used by Health Canada for the conduct of nonclinical studies (See Appendix B). In circumstances where more detailed product specific guidance is required or where there are unique circumstances, sponsors are encouraged to consult Health Canada.

The timing of nonclinical studies, in relation to the inclusion of women of childbearing potential or pregnant women in clinical trials, should be carefully considered because of the potential for teratogenic effects of therapeutic products. Health Canada supports the harmonized requirements for nonclinical studies and the timing of these studies as outlined in ICH M3 R2: Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals, June 2009.

Assessment of embryo-fetal development can be deferred until before Phase III for women of childbearing potential using precautions to prevent pregnancy in clinical trials. Where abnormalities of reproductive organs or their function (spermatogenesis or oogenesis) have been observed in experimental animals following the administration of a substance, the
decision to include subjects in a clinical trial should be based on a careful risk-benefit evaluation. This decision should take into account factors such as the abnormalities, the dosage needed to induce them, the consistency of the findings across species and their potential reversibility, the disease being treated, the availability of alternative therapies, and the proposed duration of the trial, and/or the treatment.

2.2. Design considerations in the conduct of clinical trials

Where therapeutic products are to be used by both women and men, the potential for sex-related differences in response to these products should be identified and assessed, since such differences may affect the safety and/or efficacy of the product.

Signals of potential clinically relevant differences by sex should be identified and analyzed throughout the entire clinical development program. Signals can be identified from a variety of sources: knowledge about differences between men and women in the manifestation and prevalence of a condition; data from nonclinical studies to indicate there may be sex differences; known sex differences in pharmacokinetics (PK) and pharmacodynamics (PD) and/or in efficacy or safety of a therapeutic product of a similar class to the therapeutic product under investigation. In addition to the above, signals from early phase clinical studies/trials should guide the design and data analysis for subsequent clinical studies/trials to assess whether there are clinically relevant differences between women and men in response to therapeutic products. Such differences should ultimately be reflected in the product information.

Sponsors are encouraged to consider the following elements in the conduct and design of clinical trials:

- Both women and men should be included in all phases of clinical trials, including early phases. Inclusion of both women and men in early phase trials would enable identification of potential sex-related differences in drug metabolism, which may have implications for differences in drug response. Early phase trials may suggest potential differences by sex, or uncertainty regarding whether or not differences exist, for follow-up in subsequent studies. This may not be possible or feasible for each product. In such instances, there should be a plan to develop the information needed.

- Health Canada notes that while initial safety studies on a new drug are usually conducted in healthy volunteers, trials may be conducted in patients when administration of the drug to healthy volunteers is not ethical. Inclusion of women of child bearing potential in these early phase trials involves a consideration of the risk/benefit ratio for a healthy female volunteer exposed to a potentially embryotoxic therapeutic product, relative to a female with a serious or life-threatening condition. The Informed Consent document should include sufficient information regarding the potential risks to inform women so

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6 PK/PD studies are not relevant to medical devices.
7 See also ICH E9: Statistical Principles for Clinical Trials. February 1998.
8 Health Canada Guidance for Clinical Trial Sponsors, Effective date 2003/06/05; Administrative Changes Date 2009/03/12
that they may make informed decisions about the potential risks and benefits of the therapy and the trial.

- The timing for inclusion of women in clinical trials, (including the timing for inclusion of women of childbearing potential) and the use of pregnancy prevention measures should be considered when designing clinical trials. Sponsors should refer to ICH M3R2: Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals, June 2009 for additional guidance on the timing of trials.

- Physiologic differences between men and women may have implications for dose-finding studies, generally carried out in Phase I and early Phase II, and for analysis of adverse events\(^9\). In this regard, dose-finding, pharmacokinetic and pharmacodynamic studies should include both men and women, in order to identify any potential sex-related differences in dose-response (i.e., women may require larger or smaller doses or different time courses than men to see a similar effect) and/or safety. If data from early studies suggest the presence of a potential clinically significant sex-related difference, sponsors are recommended to consider the result for hypothesis testing in subsequent trials. Subsequent studies need to be designed to determine if sex differences are meaningful and clinically relevant. For Phase III confirmatory studies in particular, subgroup analysis may be pre-specified and, ideally, be powered to accommodate these early findings.

- If data from early phase trials do not indicate potential sex-related differences, it cannot be assumed that clinically relevant differences do not exist. It is therefore recommended that the statistical section of the study protocol for Phase III trials include pre-specified plans for assessing sex related differences on efficacy and safety. The pre-specified plans for assessing such differences should be carried out once the overall treatment effect has been shown to be significant. Post hoc analysis to assess sex related differences should only be carried out in trials that are already completed or ongoing, and the analysis should be labeled as post hoc. In addition, if there are scientific reasons to suggest the potential existence of sex related differences, stratification by sex at the study design stage should also be considered. Where possible differences by sex are identified based on this analysis, this would be hypothesis generating and signal a need for further study prior to marketing\(^10\).

In cases where it is determined that additional data is required to assess sex related differences, and when such data is to be provided post-approval, Health Canada encourages that post-market studies be implemented and conducted in a timely manner, and that the studies be designed appropriately, so as to provide as definitive an answer as possible, to the question of sex related differences.

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\(^9\) Research indicates that there can be differences between men and women in adverse drug effects, and that women may be more prone to adverse events than men.

\(^10\) The findings of analysis to assess sex-related differences may be discussed with the regulator.
In the context of a drug submission\textsuperscript{11}, it is recommended that sponsors carry out and present an analysis to assess the influence of sex in the submission where data indicate that sex differences are a consideration, or where the product belongs to a class where sex differences are known. This analysis should be carried out for individual studies, as well as in the integrated analysis of efficacy and safety. A meta-analysis of the data from the various trials can be considered to assess the clinical significance of sex-related differences.

Where sex-related differences in therapeutic product response are identified, it is important to confirm the reasons for these differences (e.g. whether they are related to organ size/weight, physiological differences, including but not limited to pre- or post-menopausal state, or potential route of administration, dose, dosing regimen, dosage form or product formulation), in order to determine how to mitigate the effect of sex-related differences in the clinical setting, as appropriate.

Relevant findings as outlined above, with respect to sex differences in response to therapeutic products, should be reflected in the product monograph in each appropriate section and/or subsection.

2.3. Enrolment of women in clinical trials: Considerations related to informed consent, including pregnancy prevention

2.3.1. Informed Consent

Sponsors must ensure that subjects provide their free and informed consent to enroll in a clinical trial, consistent with provisions outlined in applicable regulations and guidelines.

- For drugs, these are the Food and Drug Regulations [C.05.010 (h)] and ICH E6 GoodClinical Practice (4.8 Informed Consent of Trial Subjects).
- For medical devices, these are the Medical Devices Regulations [81.(k)(ii)] and ISO 14155 standard, Clinical Investigation of Medical Devices for Human Subjects.
- For natural health products, these are the Natural Health Products Regulations [4.74(h)] and ICH E6 Good Clinical Practice.

This consent must be documented, in writing, and include disclosure of all relevant information, including the risks and anticipated benefits of the research to the subject, if any, and other information necessary for a person to decide whether or not to participate.

As part of the regulatory requirement for the ethical conduct of a clinical trial, fully informed consent is needed. Sponsors have an obligation to fully inform clinical trial subjects, both female and male, in addition to all other risks, about (a) the potential risks of reproductive and foetal toxicity, including teratogenicity; and about (b) pregnancy prevention, so that prospective

\textsuperscript{11} The Natural Health Products Directorate reviews Product License Applications (PLAs) using its own regulatory framework.
subjects understand how and when to take precautions to prevent pregnancy in the context of a trial.

The Informed Consent Form and the Investigator’s Brochure should include all available information regarding the potential risk of foetal and reproductive toxicity. However, if the study excludes pregnant or breastfeeding women, and requires the use of birth control during the entire trial and a period after the trial is over, the emphasis on the potential foetal and reproductive toxicity may be reduced. While animal models cannot always predict all possible human toxicities, if animal reproductive toxicity studies are complete, the results should be presented with an appropriate explanation of their significance in humans.

If foetal and reproductive toxicity studies have not been completed other pertinent information should be provided, such as a general assessment of foetal toxicity in therapeutic products with related structures or pharmacologic effects. If relevant information is not available from reproductive toxicity studies, the Informed Consent Form as well as the Investigator’s Brochure should explicitly note that the potential for reproduction and embryo-foetal risk cannot be excluded.12

It is also expected that adequate counseling will be provided to subjects concerning what is known or not known about foetal and reproductive toxicity, and about the importance of using a reliable method of contraception. Clinical trial subjects should also be apprised of procedures in place, should inadvertent pregnancy occur in the context of a trial.

If further information about reproductive and foetal toxicity about a product under investigation (including teratogenic effects) becomes available during the course of a clinical trial, this additional information should be provided to clinical trial subjects (via updated informed consent). Equally, the clinical trial investigator and the regulator should be notified.

2.3.2. Pregnancy prevention / contraception

In accordance with good clinical practice, clinical protocols should include measures to minimize the possibility of foetal exposure to the investigational product when the investigational product has been estimated to pose a risk to the health of the foetus and/or the pregnant woman. Precautions include:

(i) **Use of reliable method(s) of contraception** (See also Appendix A), and/or abstinence, for the duration of therapeutic product exposure. When the product under investigation (e.g. drug or natural health product) may lessen the effectiveness of a hormonal contraceptive agent, clinical trial subjects should be advised to use an additional non-hormonal method of

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12 ICH E6 4.8 ‘Informed Consent of Trial Subjects’ provides details pertaining to these matters, including specific areas that should be covered in “the informed consent discussion and the written informed consent form and any other written information to be provided to subjects...” and, ICH M3R2 speaks to an informed consent process “based on any known pertinent information related to reproduction toxicity, such as general assessment of potential toxicity of pharmaceuticals with related structures or pharmacological effects. If no relevant reproductive information is available, the potential for risks should be communicated.”
contraception (e.g. double barrier methods) for the duration of the exposure. Information on the duration of contraception beyond the study period should be provided to subjects.

(ii) **Initial pregnancy testing** prior to participation in the clinical trial and, where necessary and appropriate, study entry only after a confirmed menstrual period. If pregnancy is confirmed prior to the start of the trial in general, the subject should not be enrolled in the trial. Exceptions may be considered on a case by case basis (e.g. cancer patients fully informed about the foetal risks).

(iii) **Additional pregnancy testing**, as necessary and appropriate, at predetermined intervals, based on risks and benefits. Considerations may include the length of the trial, the subject population and the specific product.

Where required, contraception should be extended beyond the last dose of the investigational product. The duration will differ by product (e.g. length of half-life) and will depend on what is known and not known about the product with respect to reproductive toxicity. The duration required will also depend on the pharmacokinetics/pharmacodynamics of the product and will usually be longer for biologics than for pharmaceuticals.

### 2.4. Inadvertent pregnancy in clinical trials

Despite precautionary measures to prevent pregnancy in clinical trials (See Section 2.3), pregnancies do occur, and can happen at any stage of a clinical trial.

Health Canada recognizes that inadvertent pregnancy within a clinical trial is an important issue about which there is limited guidance internationally\(^{13}\). The following recommendations are offered for the management and follow-up of an inadvertent pregnancy, should it occur in the context of a clinical trial and when it is estimated that the investigational product poses a risk to the health of the foetus and/or the pregnant woman:

- Subjects (female and male) should be advised to report, immediately, to the Investigator a suspected or confirmed pregnancy that occurs in the course of a clinical trial (including during any period of exposure that may exceed the length of the trial).

- In addition to preventing and minimizing the risk of inadvertent pregnancy in a clinical trial, sponsors should have documented procedures for investigators to follow in case an inadvertent pregnancy occurs in the course of a clinical trial (including for any duration of exposure that may exceed the length of the trial).

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\(^{13}\) ICH E8 *General Considerations in Clinical trials states*: “If a patient becomes pregnant during administration of the drug, treatment should generally be discontinued if this can be done safely. Follow-up evaluation of the pregnancy, foetus, and child is very important.” In addition, ICH E2A requires sponsors to report serious and unexpected adverse drug reactions, including a congenital anomaly/birth defect.
If an inadvertent pregnancy occurs in the course of a clinical trial, treatment should generally be discontinued if this can be done safely and the pregnant subject withdrawn from the trial. However, exceptions may be considered on a case by case basis where the benefits to the subject of continuing in the trial clearly outweigh the risks to the foetus (e.g. cancer patients fully informed about the foetal risks).

Follow-up procedures regarding the course of the pregnancy should be discussed with the subject, as appropriate. Follow-up is recommended throughout the pregnancy and for an appropriate period thereafter, when the pregnancy results in a live birth, and is subject to the woman’s consent.

The outcome of each pregnancy should be recorded and followed-up. For live births, longer term follow-up of a child is recommended, when possible and appropriate. It is recognized that the decision to follow up in the longer term, and the specific time frame for follow-up may vary with what is known, or not known about the reproductive and teratogenic risks of the product or class of products and other factors. In this regard, outcome data of foetal exposure comprise both structural malformations (typical birth defects) that are often, but not always, detected in the neonatal period, and non-structural or longer-term functional effects that are not easily detected in the immediate neonatal period. Some cardiac, renal and intestinal malformations are not always diagnosed immediately postpartum, and data regarding the incidence of these malformations is significantly influenced by duration of follow-up and availability of diagnostic tests.

Where congenital anomaly/birth defect occurs in the context of a clinical trial, sponsors are required to report this to the regulator within 15 days of becoming aware of the event. Spontaneous abortion within the context of a clinical trial should also be reported to the regulator within 15 days. This information will also need to be captured in any safety update provided on the product, throughout its development.

2.5. Inclusion of pregnant and breastfeeding women in clinical trials

Pregnant and breastfeeding women are generally excluded from clinical trials because of real or perceived harm to the woman, the developing foetus and/or the infant. As a result, only limited information is available about effects of therapeutic products used by these populations to inform health care decisions.

Health Canada recognizes the need for reliable information to advise on the use of therapeutic products during pregnancy and breastfeeding. Many women use therapeutic products during pregnancy and when breastfeeding for treatment of chronic conditions, or for conditions that arise during pregnancy, despite lack of evidence for safety or efficacy. In addition, some women may become pregnant while on medication.

The inclusion of pregnant and/or breastfeeding women in pre-market trials is encouraged when it is considered safe for the women, developing fetus and/or infant based on the guidance below. Post-market surveillance or clinical trials may be alternative or additional ways of gathering data.
In the following sub-sections, 2.5.1 provides information related to including pregnant women in clinical trials, while 2.5.2 provides considerations for including breastfeeding women in clinical trials.

2.5.1. Considerations for including pregnant women in clinical trials

A decision to enrol pregnant women in a specific trial should be individualized and based on a careful risk/benefit assessment taking into consideration: the nature and severity of the disease; the availability and results of previous nonclinical data on pregnant and non-pregnant animals, and results from clinical data; the availability of alternative therapy/therapies and knowledge about their associated risks; the stage of pregnancy in relation to overall development of the foetus, especially regarding foetal brain development; and the potential for harm to the woman, the foetus or child.

A key consideration in the study of therapeutic products used by pregnant women will be follow-up of the pregnancy, foetus and child. Longer term follow-up of a child is recommended when possible.

The inclusion of pregnant women in clinical trials should be considered when:

(i) The specific use of the therapeutic product is for pregnant or breastfeeding women (e.g. for obstetrical or pregnancy related problems).

(ii) The studies are of agents that can be expected to address an unmet, or inadequately met, health need for pregnant women and/or foetuses (e.g. pregnant women with HIV; other life threatening conditions).

(iii) The studies are of agents which can be expected to improve pregnant women and/or foetal outcomes as compared to existing therapy.

(iv) Animal studies have been conducted, including studies on pregnant animals, and there is data on non-pregnant women on which to base an estimate of risk to the woman and/or foetus.

(v) For a new drug or new indication there is anticipated or actual use of the drug in pregnant women and women of childbearing potential.

(vi) Research involving pregnant women should be research of potential health benefit to pregnant women or the foetus. Any potential benefit to foetuses should be weighed against possible risks to the pregnant women.

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(vii) The risk to the foetus is not greater than that from established procedures routinely used in an uncomplicated pregnancy, or in a pregnancy with complications comparable to those being studied, and the purpose of the research is the development of biomedical knowledge which cannot be obtained by any other means.

The woman has to be fully informed of the risks to her, the foetus and the newborn. This condition will apply to any of the preceding circumstances.

Pharmacokinetic studies\(^{15}\) may be conducted in pregnant women, where, in addition to the above-noted considerations, the consequences of under or overdosing in pregnancy are great (e.g. narrow therapeutic range drugs, cancer chemotherapy) and/or pregnancy is likely to alter significantly the PK of a therapeutic product (e.g. drugs excreted by the kidneys). However, pharmacokinetic studies in pregnant women should not be conducted if the therapeutic product will not be used in clinical practice or it is known, or suspected, to have high risk to the foetus.

### 2.5.2. Considerations for including breastfeeding women in clinical trials

Studies in breastfeeding women include, but are not limited to, studies that measure the effects of a therapeutic product on milk production and composition, studies to determine whether the therapeutic product is present in human milk, or studies to determine whether dose adjustments are required during breastfeeding, as well as implications for the baby (e.g. impact on growth and/or development; severity/frequency of adverse events). The inclusion of breastfeeding women in clinical trials should be considered when:

(i) A new indication is being sought for an approved therapeutic product and there is evidence of use or anticipated use of the therapeutic product by breastfeeding women;

(ii) After market authorization, use of a therapeutic product in breastfeeding women becomes evident (e.g. via reports in the medical literature, general media, anecdotal information or adverse event reports);

(iii) There is concern that the consequences of uninformed dosages for use while breastfeeding are potentially serious and/or severe. This includes the following circumstances:

- A therapeutic product is under review for market authorization and is expected to be used by women of reproductive age;
- Marketed medications that are commonly used by women of reproductive age (e.g. antidepressants, anti-hypertensives, anti-infectives, anti-diabetics and analgesics);

(iv) The risk to the infant or mother is not greater than that from established procedures routinely used during breastfeeding, is comparable to those being studied, and the purpose of the research is the development of biomedical knowledge which cannot be obtained by any other means.

\(^{15}\) While it is recognized that there may not always be a direct benefit to a pregnant women or her foetus by participating in a pharmacokinetic study, there is an expectation that it will lead to the development of important biomedical knowledge that cannot be obtained by any other means.
2.5.3. Post-market studies

As with pediatrics and other populations, it is anticipated that most studies regarding the safety and efficacy of therapeutic products in pregnant or breastfeeding women will be carried out following initial marketing for use in the general population. Health Canada strongly encourages the gathering of data on pregnant and breastfeeding women. This would include monitoring the outcome of a pregnancy with regard to the health of the woman and child, in the short and longer term. Methodologies for gathering information may include but are not limited to: observational studies; pregnancy registries and cohort studies; case control studies; case reports; database linkages; and interventional studies such as pharmacokinetic studies and foetal therapy studies.

Because of the size of the populations included in clinical trials in the pre-market stage, the information that results does not cover all aspects of the use of a drug product. Therefore, post-market studies are important to further inform health care decisions where pregnant and breastfeeding women are concerned. Post-market studies are also important to manage all aspects of the life-cycle of a drug and to be able to maintain current each therapeutic agent's benefits and risks.

There are circumstances in which consideration should be given to include pregnant or breastfeeding women in clinical studies, including clinical trials. In the vast majority of cases, studies will be conducted in pregnant or breastfeeding women already prescribed and taking the medication.

Gathering information from clinical studies where pregnant and/or breastfeeding women are included would confirm whether or not the therapeutic product crosses the placenta in humans and/or whether or not the product is excreted in milk.

2.5.4. Consultation with Health Canada

Where relevant Guidance documents (and Draft Guidance) issued by the U.S. Food and Drug Administration and the European Medicines Agency are referenced in the design and conduct of clinical studies that include pregnant and breastfeeding women, Health Canada’s Health Products and Food Branch should be consulted prior to undertaking these studies to seek information on what is acceptable in the Canadian context.

2.6. Considerations specific to medical devices

While some medical devices are sex specific (e.g. condoms, prostate cancer treatment for men; pregnancy test kits and intra-uterine contraceptive devices for women), the vast majority of medical devices are intended for use by both men and women. These include orthopaedic implants, interventional cardiology devices, diagnostic imaging instruments, various implants such as those for use in ophthalmology and in-vitro diagnostic devices.

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16 Guideline 17, The Council for International Organizations of Medical Sciences (CIOMS)
As with other therapeutic products, where medical devices are to be used by both women and men, clinical investigations should be designed to identify whether there are differences by sex that affect the safety and efficacy of the device, including the nature and extent of those differences.

Because of the invasive nature of many medical devices, testing in healthy volunteers does not usually occur. This necessitates the use of nonclinical, including animal, model testing to help assess the preliminary safety and performance of these medical devices.

Protocols should address any known or foreseeable factors that may affect outcomes or interpretation of results. These may include subject related factors such as age, sex or lifestyle. The methods for addressing these factors in the investigation, including for example, subject selection, investigation design (e.g. stratified or randomized), or statistical analysis should be described.

Initial human clinical investigations with devices involve small pilot studies with patients as subjects. Where the pilot studies indicate the concept is feasible, these would be followed by larger studies with well-designed protocols. Ideally, these studies should be powered for subgroup analysis, where appropriate, to be able to draw valid conclusions about sex differences in response to medical devices.

Where study size does not support meaningful subgroup analysis, post-market follow-up should be considered.

2.7. Considerations specific to natural health products

The principles and overall guidance presented in this Guidance Document also generally apply to clinical trials investigating natural health products. These include pharmacokinetic, pharmacodynamic, bioequivalence, safety, and efficacy studies of NHPs, alone or in combination with other therapeutic products or procedures. Breastfeeding and/or pregnant women should be considered for inclusion in these study designs provided that the evidence supports the safe use of the investigational NHP in these populations, and/or when the potential benefit for the woman, foetus or child outweighs the risks associated with the investigational intervention.

Research shows that women use NHPs more than men. Research shows that women use NHPs more than men.\(^{17}\) There is also widespread use of NHPs during pregnancy, breastfeeding and in childhood/adolescence.

The common usage of NHPs by the Canadian public and particularly by participants in clinical trials investigating pharmaceutical drugs should be taken into account when designing drug trials due to possible effects on safety and efficacy from potential drug-NHP interactions or confounding treatment effects\(^{18}\). Study participants should be questioned about NHP use, and

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\(^{17}\) Ipsos-Reid Baseline Natural Health Products Survey Among Consumers. Submitted to Health Canada, March 2005.

\(^{18}\) NHP- drug interactions constitute only one subset of a general consideration of therapeutic product interactions in the design of clinical trials or in post-market follow up.
given advice on any restricted use, since they may not otherwise consider this information relevant to the study.

Certain NHPs may decrease the effectiveness of hormonal contraception (See also Appendix A).

The *Natural Health Products Regulations* (Part 4) have provisions for reduced pre-clinical and PK/PD evidence requirements in the Investigator’s Brochure for the conduct of clinical trials of certain natural health products that have a long history of use in humans.\(^{19,20}\)

It is to be noted, that some clinical trials of natural health products and natural systems of medicine do not easily lend their methodology to randomization or blinding, and in certain cases the role of the practitioner is a key in the intervention (e.g., homeopathic medicine, traditional Chinese medicine, etc.).

### 3. RISK MANAGEMENT AND PHARMACOVIGILANCE PLANNING

Health Canada adopted the International Conference on Harmonization guideline, *E2E Pharmacovigilance Planning* \(^{18}\) (ICH E2E). ICH E2E identifies topics that should be incorporated into the safety specifications and risk management plan/pharmacovigilance plan to clarify where further evidence/data may be needed post-authorization of a therapeutic product. Sex-based differences or considerations should be addressed within these topics. This could include information related to differences between men and women in their response to therapeutic products, as well as reproduction/developmental toxicology or the use of products by special populations including pregnant and breastfeeding women.

Further, any gaps in knowledge related to sex-based potential differences or considerations and any further post-authorization evaluation requested by the regulator should be made public at the time of approval.

### 4. EFFECTIVE DATE

This guidance document is effective as of May 29, 2013.

### 5. CONTACT INFORMATION

Questions concerning inclusion of women in clinical trials and analysis of sex differences should be directed to:

Office of Policy and International Collaboration  
Biologics and Genetic Therapies Directorate  
Health Products and Food Branch  
Health Canada  
200 Tunney’s Pasture Driveway

\(^{19}\) Part 4, *Natural Health Products Regulations*, Section 66(e)  
APPENDIX A: Considerations in using contraceptives in clinical trials

Preamble:

In conducting clinical trials, contraceptive guidance is frequently necessary and may involve complex considerations to address the needs and circumstances of a diversity of subjects and their partners. Compliance may be enhanced when both male and female subjects and their sexual partners have a clear understanding about the importance of contraception and about methods that should be used consistently and correctly. In addition to pregnancy testing prior to and during a clinical trial, “subject education should be sufficient to ensure compliance with measures designed to prevent pregnancy during the period of drug exposure (which could exceed the length of the study)\(^2\)."

Much knowledge regarding contraception is publicly available (see suggested resources section below). This Appendix is intended to be an additional resource to clarify some considerations in using contraceptives in clinical trials.

*Note: No one method of contraception is 100% effective.* It is recommended that a statement to this effect be included in all Informed Consent Forms requiring contraceptive guidance. The Informed Consent Forms should also provide a list of the contraceptive methods recommended. In addition, Informed Consent Forms should clearly state if there is a possibility that the investigational product may lessen the effectiveness of a hormonal contraceptive agent.

I. Relevant Populations

I. a. Studies that include Women

Contraception should be considered in women of childbearing potential

Women of childbearing potential are females who have experienced menarche and do not meet the criteria for women Not of childbearing potential. Women Not of childbearing potential are females who are permanently sterile or postmenopausal. Postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause.\(^2\)

I. b. Studies that include Men

Abstinence or contraception may be recommended where there is evidence (or good reason to believe) that the investigational product binds to the sperm and may have teratogenic effect.

I. c. Studies that include Paediatric Subjects

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\(^2\) Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization, ICH M3R2, 2009

Studies in paediatric populations where it is possible that subjects (both male and female) are sexually active and have reached puberty, should contain guidance on contraception. Guidance should be provided in a manner and format appropriate to the age of the subjects.

II. Contraceptive Methods

II. a. Highly effective methods of contraception, when used consistently and correctly, result in low failure rates\(^2^3\). These may include: hormonal contraceptives (e.g. combined oral contraceptives, patch, vaginal ring, injectables, and implants); intrauterine device (IUD) or intrauterine system (IUS); vasectomy and tubal ligation.

Highly effective methods of contraception might not always be achievable in the clinical trial setting and, therefore, the most effective alternative can be achieved using methods in combination.

II. b. Effective methods may include: barrier methods of contraception (e.g. male condom, female condom, cervical cap, diaphragm, contraceptive sponge).

Note:
- No barrier method by itself achieves a highly effective standard of contraception.
- The proper use of diaphragm or cervical cap includes use of spermicide and is considered one barrier method.
- The cervical cap and contraceptive sponge are less effective in parous women.
- The use of spermicide alone is not considered a suitable barrier method for contraception.

When used consistently and correctly, “double barrier” methods\(^2^4\) of contraception (e.g. male condom with diaphragm, male condom with cervical cap) can be used as an effective alternative to the highly effective contraception methods described above. The consistent and correct use of a male condom in association with spermicide may be considered an acceptable barrier method in some clinical trial settings.

III. Additional considerations

III. a. Drug-Drug/Drug-NHP Interactions:

Therapeutic products may interact with hormonal contraceptives to reduce contraception effectiveness (e.g. gastrointestinal symptoms associated with the study product may lead to lower blood levels of oral hormonal contraceptives). Considerations in drug-drug/drug-NHP interactions include: investigational drug interaction with hormonal contraception; interaction of other study drug(s) with hormonal contraception; and interaction of concomitant drug(s) with

\(^2^3\) According to ICH, highly effective methods are defined as “those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly.” ICH M3(R2).

\(^2^4\) A “double barrier” method refers to simultaneous use of a physical barrier by each partner. This differs from the concept of “double methods” of contraception.
hormonal contraception (e.g. prescription and over the counter medication). The use of certain natural health products may also reduce contraceptive effectiveness.

II. b. Toxicity

Use of therapeutic products where reproduction toxicity is known [i.e. studies in animals or humans have demonstrated foetal abnormalities (e.g. thalidomide), or there is evidence of foetal risk based on adverse reaction reports]: In these circumstances, the use of two forms of contraception are recommended. This includes at least one form of highly effective and one effective method of contraception.

Use of therapeutic products where the risk of foetal abnormality is not known or is unclear (e.g. lack of adequate reproduction toxicity data): In these circumstances, at least one highly effective method of contraception or two forms of effective contraception methods are recommended.

III. c. Duration of contraceptive use:

The onset of contraceptive effectiveness is method-dependent since some contraceptive methods are effective immediately while the effectiveness of others is delayed (e.g. hormonal contraceptives; vasectomy). The use of contraceptive methods by both women and men should be considered for the entire duration of the study and for an acceptable period afterwards.

Duration of contraception beyond the study period may vary by product and depends on factors including the product half-life (duration of contraception is often longer for biologics); previous evidence of toxicity to the foetus or semen; or where the impact of the therapeutic product with respect to reproduction toxicity is unknown.

Suggested Resources


APPENDIX B: ICH Guidelines


- For Nonclinical Studies See *Safety Topics*
- For Clinical Studies See *Efficacy Topics*

Additional International Guidance for Nonclinical Studies:

APPENDIX C: Bibliography


Food and Drug Regulations - Amendment (Schedule No.1024) Clinical Trial Framework. 2001.

Government of Canada, Health Portfolio Sex and Gender Based Analysis Policy. 2009.


International Conference on Harmonisation, ICH E8: General Considerations in Clinical Trials, 1998.


Ipsos-Reid Survey for Health Canada, Baseline Natural Health Products Survey Among Consumers. 2005.

