

Health Canada GUIDANCE DOCUMENT

“Considerations for Inclusion of Women in Clinical Trials and Analysis of Data by Sex”

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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.

1. INTRODUCTION

1.1 Policy Objectives

The intent of this document is to provide guidance for sponsors in the conduct and design of clinical trials to identify sex-related differences in response to therapeutic products and to generate evidence to advise the optimal use of therapeutic products in women and men. Specifically, this guidance addresses considerations pertaining to the appropriate inclusion of women in all stages of clinical trial research in order to identify and analyze sex-related differences that may affect the safety and efficacy of a therapeutic product.

This guidance 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 addresses health differences between men and women, boys and girls¹.

This guidance document supercedes the Health Canada Guidance Document *on Inclusion of Women in Clinical Trials* issued in 1997.

1.2 Principles

This guidance 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* (1998) where it states that "women shall not automatically be excluded from research solely on the basis of sex or reproductive capacity" (Article 5.2).

1.3 Policy Statements

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 be composed of subjects representative of the population(s) that the sponsor expects will use the therapeutic product. Alternatively, the sponsor should provide justification, including clear scientific rationale for not doing so,

¹ Government of Canada's Health Portfolio Sex and Gender Based Analysis Policy. 2009.

that is acceptable to Health Canada.

- It is recommended that a representative number of women be included into clinical trials for therapeutic products that are intended to be used specifically by women or in heterogeneous populations that include women.
- It is recommended that women, including those of child-bearing potential and postmenopausal women be included, at the earliest 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; and product-disease) can be identified and assessed.

1.4 Scope and Application

1.4.1 This guidance applies to research of 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.

1.4.2 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.

1.4.3 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 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.

The guidance also addresses considerations pertaining to pregnant or breastfeeding women and to sexual partners of clinical trial subjects.

1.4.4 While the main focus is on women in clinical trial research of therapeutic products, some considerations pertinent to men who are clinical trial subjects are also addressed.

1.5 Background

A review of Health Canada's Guidance Document on the Inclusion of Women in Clinical Trials was identified as a key initiative in the report *Clinical Trials Regulatory Review: Targeted Measures for a Strengthened Framework*, Health Products and Food Branch, (2008).

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). These pharmacokinetic differences are theorized to stem from variations between the sexes in factors such as body weight, plasma volume, gastric emptying time, plasma protein levels, CYP activity, 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, 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 recognizes that there is a need to develop the information base concerning differences between men and women in their response to therapeutic products and regarding therapeutic products used in pregnancy and while breastfeeding. Analysis of clinical trial data by sex can identify where there may be clinically relevant sex-related differences in therapeutic response in order to minimize the risks, maximize benefits and promote the optimal use of therapeutic products in women and men. Increased information on the safety and efficacy of products used in pregnancy or while breastfeeding can inform health care decisions.

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

- To clarify the scope of the original guidance, including the populations to which it applies;
- To provide further guidance to sponsors on issues not addressed or minimally addressed in the 1997 guidance document. These include: inadvertent pregnancy in the course of a clinical trial and inclusion of pregnant and breastfeeding women in clinical studies/trials;
- To 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;
- To provide guidance within the current regulatory environment.

This guidance encourages the generation and consideration of new scientific knowledge about sex differences, and about therapeutic products used in pregnancy and 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 the post-marketing stage.

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 where appropriate, in safety.

In some instances, it may be appropriate to conduct confirmatory studies in a single sex, for example, where the product is intended for use by women or by men only, or to evaluate the effects of phases of the menstrual cycle on therapeutic product response in females. Furthermore, for studies conducted to demonstrate the relative *in vivo* performance of different formulations

such as comparative bioavailability studies, enrolment of subjects from a single sex may be justified.

2.1 Nonclinical Studies

2.1.1 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 2.2)

2.1.2 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 with Health Canada.

2.1.3 The timing of nonclinical studies in relation to inclusion of women of childbearing potential or pregnant women in clinical trials is an important consideration because of the potential for teratogenic effects of therapeutic products. 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. Health Canada supports the harmonized requirements for non clinical 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*.

2.1.4 Where abnormalities of reproductive organs or their function (spermatogenesis or oogenesis) have been observed in experimental animals following 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 the abnormalities, the dosage needed to induce them, the consistency of the findings across species, the disease being treated, the availability of alternative therapies, and the proposed duration of the trial and/or the treatment.

2.2 Enrolment of Subjects in Clinical Trials: Considerations Related to Informed Consent, including Pregnancy Prevention

Informed Consent

2.2.1 Sponsors must ensure that subjects provide their free and informed consent to enrol 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 Good Clinical Practice (4.8 Informed Consent of Trial Subjects).
- For medical devices, these are the *Medical Devices Regulations* [81.(k)(ii)] and ISO 14155 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.

2.2.2 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.

2.2.3 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 male², about (a) the potential risks of reproductive and foetal toxicity, including teratogenicity; and about (b) pregnancy prevention so that prospective subjects understand how and when to take precautions to prevent pregnancy in the context of a trial.

2.2.4 The Informed Consent Form and the Investigator's Brochure should include all available information regarding the potential risk of foetal and reproductive toxicity. While animal models can not 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, including a theoretical or confirmed risk of teratogenesis.

2.2.5 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 and Investigator's Brochure should explicitly note that the potential for reproduction and embryo-foetal risk cannot be excluded.³

2.2.6 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

² Male subjects should be made aware of potential risk so the offspring should a female partner be exposed to an agent prior to or around the time of conception and/during pregnancy

³ 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.*"

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.

2.2.7 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.

Pregnancy Prevention / Contraception

2.2.8 In accordance with good clinical practice, clinical protocols should include measures to minimize the possibility of foetal exposure to the investigational product. Precautions include:

(i) **The use of reliable method(s) of contraception** (See 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 contraception for the duration of the exposure. It is also advisable for CT subjects to be informed when it is considered safe for a woman to become pregnant after the last dose of the investigational therapy.

(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.

2.2.9 It is best to extend the duration of contraception, where needed, beyond the last dose of the investigational therapy. 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. Duration required will also depend on the PK/PD of the product and is usually longer for biologics than for pharmaceuticals. (Appendix A)

2.3 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)⁴ 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 product information.

Sponsors are encouraged to consider the following elements in the conduct and design of clinical trials:⁵

2.3.1 The inclusion of both women and men 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.

2.3.2 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 ethical⁶. 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.

2.3.3 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* and Section 2.1.3 of this Guidance regarding the timing for inclusion of men and women in clinical trials, (including timing for inclusion of women of childbearing potential). Section 2.2 of this Guidance regarding informed consent and pregnancy prevention measures also applies.

2.3.4 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 events⁷. 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

⁴ PK/PD studies are not relevant to medical devices.

⁵ See also ICH E9: Statistical Principles for Clinical Trials. February 1998.

⁶ Health Canada Guidance for Clinical Trial Sponsors, Effective date 2003/06/05; Administrative Changes Date 2009/03/12

⁷ 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.

particular, subgroup analysis may be pre-specified and ideally be powered to accommodate these early findings.

2.3.5 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 recommended that post hoc analysis of the data by sex be carried out in Phase III trials. 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, or monitoring post-market. Health Canada supports the use of post-market data collection where confirmatory trials generate signals or hypotheses about potential sex-related differences.

2.3.6 In the context of a drug submission⁸, 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.

2.3.7 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, 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.

2.3.8 Relevant findings with respect to sex differences in response to therapeutic products should be reflected in the product information.

2.4 Inadvertent Pregnancy

Despite precautionary measures to prevent pregnancy in clinical trials (See Section 2.2), 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 internationally⁹. The following are offered for the management and follow-up of an inadvertent pregnancy, should it occur in the context of a clinical trial.

⁸ The Natural Health Products Directorate reviews Product License Applications (PLAs) using its own regulatory framework. Section 2.3.6 would not apply to NHPs .

⁹ 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.

2.4.1 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 duration of exposure that may exceed the length of the trial).

2.4.2 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).

2.4.3 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).

2.4.4 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.

2.4.5 In the case of a live birth, 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.

2.4.6 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 Studies/Trials

Health Canada recognizes the need for reliable information to advise 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. In addition, some women may become pregnant while on medication.

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

Post-market Studies:

2.5.1 As is currently the case, 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. The use of various methodologies to gather data pertaining to the effects of therapeutic product use in pregnant and breastfeeding women is strongly encouraged. This would include monitoring the outcome of a pregnancy with regard to the health of the women and of the child, in the short and longer term.¹⁰ Such methodologies may include: observational studies, including pregnancy registries and cohort studies; case control studies; case reports; database linkages; and interventional studies such as pharmacokinetic studies and foetal therapy studies.

2.5.2 Post-marketing studies are useful but may not provide all information necessary to inform health care decisions for pregnant and breast feeding women. Clinical trials are needed to fill the gap, where appropriate.

There are circumstances in which consideration should be given to including 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, hence such studies will not further increase foetal risks.

Clinical studies in pregnant and breastfeeding women should assess whether or not the therapeutic product crosses the placenta and/or whether or not it is excreted in milk.

Considerations for Including Pregnant Women in Clinical Trials¹¹

2.5.3 A decision to enrol pregnant women in a specific trial must 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.

¹⁰ Guideline 17, The Council for International Organizations of Medical Sciences (CIOMS)

¹¹ Considerations build upon information contained in US FDA *Draft Guidance for Industry Pharmacokinetics in Pregnancy-Study Design, Data Analysis and Impact on Dosing and Labeling*, US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research October, 2004 and *Draft Guidance for Industry Clinical Lactation Studies –Study Design, Data Analysis and Recommendation for labeling*, US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, February, 2005

2.5.4 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. See also Sections 2.4.5 and 2.4.6.

2.5.5 Sponsors may consider including pregnant women in clinical studies, including clinical trials under the following circumstances:

(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 which can be expected to address an unmet maternal /foetal risk or disease (e.g. pregnant women with HIV; other life threatening conditions) and where there are no alternatives available on the market.

(iii) The studies are of agents which can be expected to improve maternal/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) The woman and/or foetus will benefit directly from participation and where any potential benefit to the foetus should be weighed against possible risks to the mother.

(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.

(viii) The woman is fully informed of the risks to her, the foetus and the newborn (see Section 2.2).

(ix) Pharmacokinetic studies¹² 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).

Pharmacokinetic (PK) studies in pregnant women are *not* recommended if the therapeutic product is not used in pregnant women or has known or highly suspect foetal risk.

¹² While it is recognized that there may not always be a direct benefit to a pregnant women or her foetus by participating in a PK study, there is an expectation that it will lead to the development of important biomedical knowledge that cannot be obtained by any other means.

Considerations for Including Breastfeeding Women in Clinical Trials

2.5.6 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. severity/frequency of adverse events).

2.5.7 Sponsors may consider including breastfeeding women in clinical studies, including clinical trials, under the following conditions:

(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) If there is concern that the consequences of uninformed dosages for use while breastfeeding are potentially great.

(iv) A therapeutic product is under review for market authorization and is expected to be used by women of reproductive age;

(v) Marketed medications that are commonly used by women of reproductive age (e.g. antidepressants, anti-hypertensives, anti-infectives, anti-diabetics and analgesics);

2.5.8 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

2.6.1 While some medical devices are sex specific (e.g. condoms, prostate cancer treatment for men; pregnancy testkits 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.

2.6.2 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.

2.6.3 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.

2.6.4 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.

2.6.5 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.

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

2.6.7 The skill of the surgeon or interventionalist is critical to outcome. To enhance the reliability of results, multicentre trials that involve a number of surgeons or interventionalists are preferred to support licencing applications for new technologies.

2.6.8 Since devices are often used in surgical procedures, there are methodological challenges in adequately randomizing patients in trials that compare standard operative procedures to new technologies and blinding is difficult where devices neither look alike nor operate alike.

2.7 Considerations Specific to Natural Health Products

2.7.1 The principles and overall guidance presented in this Guidance Document also generally apply to clinical trials investigating natural health products (NHPs).

2.7.2 Research shows that women use NHPs more than men. Survey data from 2005 suggest that 78% of women and 64% of men have used natural health products¹³. There is also widespread use of NHPs during pregnancy, breastfeeding and in childhood/adolescence.

2.7.3 The common usage of NHPs by the Canadian public and particularly by participants in clinical trials investigating pharmaceutical drugs should be taken in to account when designing drug trials due to possible effects on safety and efficacy from potential drug-NHP interactions or

¹³ Ipsos-Reid Baseline Natural Health Products Survey Among Consumers. Submitted to Health Canada, March 2005.

confounding treatment effects¹⁴. Study participants should be questioned about NHP use, and given advice on any restricted use, since they may not otherwise consider this information relevant to the study.

2.7.4 Certain NHPs may decrease the effectiveness of hormonal contraception (e.g. St. John's Wort¹⁵, soy isoflavones, phytoestrogenic herbs). (See also Appendix A).

2.7.5 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 NHPs that have a long history of use in humans.^{16,17}

2.7.6 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 factor in the intervention.

2.8 Risk Management and Pharmacovigilance Planning

Health Canada recognizes that additional information about product safety and efficacy may be needed post authorization and has indicated its intent to adopt the international Conference on Harmonization Guideline on Pharmacovigilance Planning (E2E)¹⁸. ICH E2E proposes a structure for identifying in a product submission, areas where there may be gaps in knowledge and where further evaluation may be needed post authorization. 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.

¹⁴ 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.

¹⁵ Effects of St. John's Wort on contraceptive effectiveness may vary with dosage and nature of the product.

¹⁶ Part 4. *Natural Health Products Regulations*, Section 66(e)

¹⁷ Clinical Trials for Natural Health Products Guidance Document, 2005 p. 13 http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/clini_trials-essais_nhp-psn-eng.php

¹⁸ Notice Regarding Implementation of Risk Management Planning including the adoption of ICH Guidance Pharmacovigilance Planning - ICH Topic E2E, February 2009 http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/notice_avis_rmp_pgr_e2e-eng.pdf

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)¹⁹ .

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 therapeutic product under investigation 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.²⁰ .

I.b. Studies that include Men

Contraception should be considered in men with partners of childbearing potential.

¹⁹ Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization, ICH M3R2, 2009

²⁰ See ICHM3(R2) and Canadian Consensus Conference on Menopause, 2006 Update, Journal of the Society of Gynecologists and Obstetricians of Canada, Vol. 28, Special Edition, February, 2006.

I.c. Paediatric Studies

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 rates²¹. 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” methods²² 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:

²¹ 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).

²² 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.

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 hormonal contraception (e.g. prescription and over the counter medication). The use of certain natural health products may also reduce contraceptive effectiveness. (See also Section 2.7.4)

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

William A Fisher, Amanda Black, Contraception in Canada: a review of methods choices, characteristics, adherence and approaches to counseling, *Canadian Medical Association Journal*, March 27, 2007, 176(7) p.953-961

The Canadian Society of Obstetricians and Gynecologists, Sex Sense: Canadian Contraceptive Guide, 2005.

APPENDIX B

Relevant International Conference of Harmonization (ICH) Guidance documents can be found on the ICH Website: <http://www.ich.org/>

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

Additional International Guidance for Nonclinical Studies:

WHO Guidelines on Nonclinical Evaluation of Vaccines. World Health Organization, WHO Technical Report Series, No. 927, 2005