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NOTICE

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The final version of this Health Canada guidance document **Clinical Development of Steroidal Contraceptives Used by Women** is now available. Comments and suggestions received from the consultation on the draft version of the guidance were reviewed and considered in the finalization of this document. A summary of these comments with responses from Health Canada are included in the Appendix

This and other Guidance documents are available on the **Therapeutic Products Directorate/Biologics and Genetic Therapies Directorate Website (s)** (**http://www.hc-sc.gc.ca/hpb-dgps/therapeut**). The availability of printed copies of guidance documents may be confirmed by consulting the *Guidelines and Publications Order Forms* (available on the TPD/BGTD Website) or by contacting the Publications Coordinator[1].

Should you have any questions regarding the content of the guidance, please contact

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Health Canada Santé Canada

GUIDANCE FOR INDUSTRY

Clinical Development of Steroidal Contraceptives Used by Women

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Health Products and Food Branch
Guidance Document

Canada

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FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on how to comply with the policies and governing statutes and regulations. They also serve to provide review and compliance guidance to staff, thereby ensuring that mandates are implemented in a fair, consistent and effective manner.

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 scientific 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 guidance, 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 guidances.

TABLE OF CONTENTS

1. INTRODUCTION

This guidance document addresses the development of contraceptive products, intended for use by women during their reproductive years, which contain sex steroids as active ingredient(s).

The guidances are applicable for both short-acting oral contraceptive pills containing progestin alone or pills containing a combination of progestin and estrogen, as well as long-acting products intended for contraceptive purposes such as implants, injectables, transdermal systems, intravaginal and medicated intrauterine devices (IUDs). They are not applicable to products recommended for emergency contraception.

Contraceptives are generally used by healthy women for pregnancy prevention purposes. Therefore, these products should have a very low health risk in order to be of favourable risk/benefit balance. There is a need to have a well-defined, proven contraceptive efficacy and a well-founded description of risks and adverse events to enable the user and the prescriber to make the best individual choice of a contraceptive method.

This guidance document should be used in conjunction with the Canadian *Food and Drugs Act and Regulations* and all other relevant publications.

Please consult the website in that regard: www.hc-sc.gc.ca/hpb-dgps/therapeut

2. CLINICAL PHARMACOLOGICAL STUDIES

2.1 Hormonal Activity

The chemical nature and hormonal activity of the contraceptive steroid(s) and their principal metabolites should be described. Such information may be obtained from receptor binding assays, evaluations of individual metabolites in animals (and/or humans) and studies of indicators of hormonal activity, such as SHBG (sex hormone binding globulin).

Receptor binding studies may give clues on pharmacological actions other than the estrogenic and progestagenic actions, such as influence on SHBG, as well as information on the balance between estrogenic and progestagenic/androgenic effects in women.

2.2 Pharmacological Action

The pharmacological mechanism(s), by which the contraceptive effects(s) are attained, should be well-defined. For sex steroids, such actions should include the effect on ovarian function, fallopian tubes when applicable, endometrial mucosa, cervical secretion and the hypothalamic-pituitary-ovarian axis.

2.2.1 Ovarian Function

The effects on ovarian function should be described. Methods used may include measurements of plasma concentrations of ovarian steroids and gonadotrophins and ultrasound evaluation of ovaries. At least two menstrual cycles should be studied in each participating woman.

These studies will give information on the extent to which ovarian function is suppressed by the steroids used. Ultrasound investigation will supplement the interpretation of plasma steroid determinations. It is important that sampling is frequent enough for LH, FSH, estradiol and progesterone plasma measurements so that ovulations are not missed. For a new contraceptive steroid, comparative studies should be conducted using a contraceptive with a similar mechanism(s) of action and dosage form, marketed in Canada.

In the case of a dose reduction of an already available product, comparative pharmacodynamic data should also be provided.

For the purpose of selecting an appropriate comparator, comparative pharmacodynamic data are considered useful.

For long-acting contraceptives (e.g., implants) comparative data should be provided for the entire period of intended use.

The time to onset of action, in relation to the start of treatment and dose of steroids and the time to return to normal ovarian function after discontinuation of treatment should be investigated. To be valid statistically, these need to be assessed in a sufficient number of participants. Such information is necessary for advice on the need for complementary protection at the initiation of treatment and
in case of temporary lack of compliance or voluntary interruption. This approach is indicated not only for short-acting oral contraceptive(s), but also for certain long-acting contraceptive methods.

The time of return to fertility should be followed-up in all participants who discontinue treatment due to desire to become pregnant, for as long as needed depending on the type of the study drug and results should be statistically evaluated.

2.2.2 Other Pharmacological Effects on the Reproductive System

Other pharmacological effects on the reproductive system, including endometrial changes, effects on fallopian tubes when applicable and effects on cervical mucus need to be described, especially when ovulation inhibition is not regularly attained (e.g., contraceptives containing progestin only). The study of such effects has supplementary value in explaining mechanism(s) of action, but this information is not to be used in the design, determination of the number of participants or the length of pivotal clinical trials.

2.2.3 Effects on Other Endocrine Functions

The effects on other endocrine functions (hypothalamic-pituitary, adrenal, thyroid, breast, pancreas) in women should be described. If necessary, such endocrinological effects should be investigated in details, based on pre-clinical, risk/assessment studies.

2.2.4 Metabolic and Other Important Effects

All parameters known to be affected by steroidal contraceptives including body weight, hemostasis and coagulation factors, liver, renal and cardiovascular functions should be assessed according to contemporary knowledge. Plasma lipids and carbohydrate metabolism should be evaluated with modern, state-of-the-art methods (see also Safety section). Studies must be conducted with relevant comparator(s) approved for use or marketed in Canada. For products not containing an estrogen and suppressing estrogen secretion from the ovaries, the effect on bone mineral density (BMD) and bone mineral metabolism requires investigation using validated methods.

3. EFFICACY

3.1 Study Requirements and Pregnancy Reporting

For a new contraceptive method [e.g., new steroid(s), modified steroid dosage, new route of administration], it is desirable to study a sufficient number of cycles in a large enough group of women to obtain the appropriate precision of the estimate of the contraceptive efficacy and safety.

Data for the calculation of the overall Pearl Index (number of pregnancies per 100 women years) should emanate from more than one large, well-designed, adequately controlled study.

The separate calculation of the Pearl Index for method failure requires reliable methods for recording of compliance (e.g., complete participant diaries) in order to exclude non-compliers in the denominator.

For Pearl Index calculations, in the case of short-acting oral contraceptives thirteen 28-day cycles constitute one woman year. However, for long-acting non-cyclic products (e.g., implants, medicated IUDs, etc.), one woman year equals one calendar year.
Pregnancy rates should be described by Pearl Index and Life Table analysis including all pregnancies during treatment. Reasons for premature discontinuation of the study drug should be well-documented.

The key studies need to be carried out in a sufficiently representative population (see 3.2). The study should be at least large enough to give a Pearl Index with a 95% confidence interval such that the difference between the upper limit of the confidence interval and the point estimate does not exceed one (pregnancies per 100 women years) Meeting these conditions(adequate representativeness and a precise Pearl Index) will usually require about 20,000 cycles of exposure.

In the case of short-acting oral contraceptives, pivotal trials should be of adequate length and include adequate number of participants. While efficacy of certain drug products may be established after 12 months of exposure, it is expected that a subgroup of participants in the pivotal trials will be followed for up to 2 years to adequately document both compliance and safety of the study product.

For long-acting products (e.g., implants, medicated IUDs, etc.), whose efficacy is expected to last for at least 5 years, pivotal trials should be of similar length (at least 5 years). It should be emphasized that pivotal trials must always last for the recommended

duration of efficacy. The number of participants should be sufficient to define a precise Pearl Index as mentioned above.

As drop-outs and discontinuations are inevitable in long-term clinical trials, it is recommended that planned enrollment be sufficiently large to ensure that the required number of participants complete pivotal trials.

In order to minimize drop-out rates, special care should be provided to study participants at the time of enrollment and for the duration of the study, to encourage them to complete the entire study and comply with periodically scheduled evaluations.

3.2 Demography of Women Enrolled in Clinical Studies

The demography of the group of women included in clinical trials should be comparable to that of Canadian populations. Characteristics of the study group should be carefully described, especially regarding factors thought to be relevant for the overall contraceptive efficacy of the method (e.g., weight, age, education, sexual activity, parity, smoking, alcohol use, menstrual related symptoms, concomitant use of condoms to protect from sexually transmissible diseases, concomitant use of other drugs, etc.). Because of their proven fertility, multiparous women should be preferred for participation in these clinical studies. Where heterogeneity of fertility is likely (e.g., a study group containing a subgroup of breast-feeding mothers, women advanced in their reproductive years, or those with a current or past illness compromising fertility), separate estimates of the Pearl Index should be presented for important subgroups.

Known contraindications for the use of steroidal contaceptives should be considered when selecting particpants for the clinical trials.

3.3 Need for Comparative Efficacy Studies

Studies including an active comparator are not mandatory for efficacy purposes, although they are desirable. However, for a new product utilising a mechanism of action which may result in a relatively high pregnancy rate (Pearl Index >1), comparative studies may
be necessary. In the case of a dose reduction of an already available product, comparative pharmacodynamic data should also be provided. Pharmacodynamic data may serve as

guidance information on the necessity for comparative studies. Generally, this is a requirement for methods not consistently inhibiting ovulation. When an active comparator is deemed appropriate, it should be selected from products already marketed in Canada.

For long-acting contraceptives (e.g., implants) comparative data should be provided for the entire period of intended use.

Detailed information regarding participant compliance to the proposed drug is required, including drop-out rates and reasons for discontinuation. When an active comparator has been used, similar information should be provided, along with adequate comparative analysis between the study drug and the comparator.

3.4 Reduced Requirements in Special Circumstances

In case of MINOR modifications of marketed products in Canada, requirements for the clinical studies may be reduced and consultation with the appropriate authorities of Health Canada is recommended.

As an example, a lesser number of cycles may be required provided that:

- pharmacodynamic studies show at least an equivalent effect on ovarian function comparable with the existing product.

- the reference product has a well documented efficacy and safety profile.

4. SAFETY

4.1 Amount of Safety Information

For any new steroid contraceptive, safety information should be collected from all participants who received the study drug for any length of time. The minimum amount of safety information must come from studies involving a sufficient number of women using the study drug and completing preferably two years of treatment (see 3.1). Data must be collected on bleeding events and their characteristics (frequency, amount, duration). Drop-out and discontinuation rates of studies need to be statistically analysed and reasons for these events should be reported. All laboratory tests performed should be documented
and submitted for review. Validated methodology should be used for laboratory tests and reliance on a central laboratory is recommended. A regular evaluation of all participants should

be scheduled to determine any adverse effects of the drug; use of a well-designed diary should be considered for this purpose.

- Baseline physical examinations should be conducted, and subsequently, at regular intervals throughout the clinical trials according to the following table. Any anomaly should be investigated thoroughly using, if indicated, appropriate radiological technology.
- Emphasis should be placed on changes in blood pressure, breast anomalies and modifications at pelvic exams.

- Cervical cytology should be obtained at baseline, then annually and as deemed necessary.

- Other laboratory evaluations (Haematological and Biochemical parameters) should be obtained at baseline, then every 6 months and as deemed necessary.

- All participants with abnormal results or adverse drug experiences should be followed-up.

Parameters to Study	**Clinical Assessment***				
	Baseline	**3 months**	**6 months**	**9 months**	**1 year**
Physical Exam (including blood pressure monitoring, breast and abdominal exam)	yes	yes	yes	yes	yes
Pelvic Exam	yes	-	yes	-	yes
Cervical Cytology	yes	-	-	-	yes
Laboratory Evaluation	yes	-	yes	-	yes

***** *After the first year of study drug administration, all parameters listed at 6 months should be assessed every 6 months until the completion of the study; cervical cytology should be taken annually.*

For an adequate safety assessment, whenever possible, endometrial biopsies should be obtained when the participants leave or complete the study. This endometrial biopsy is particularly important when an active component of the study drug constitutes a new chemical entity. Other circumstances which should justify the use of endometrial biopsies

are the following: women over the age of 35 years, irregular uterine breakthrough bleeding, excessive uterine withdrawal bleeding, and detected endometrial anomaly at ultrasound evaluation. Ultrasound evaluation of the endometrium cannot replace endometrial biopsy for adequate endometrium evaluation but may be complementary.

Besides the above information that must be submitted for all oral dosage forms, drugs for topical, intramuscular, subcutaneous or intravaginal administration should also be evaluated for local irritation and allergenic potential.

If the drug is to be delivered by an adhesive device, stability of adhesiveness of such device and systemic delivery of the drug must be monitored through normal daily activities such as bathing and showering.

If the drug is to be delivered by a device that should be inserted into or removed from the subcutaneous tissue, exact technique, safety measures, complication rates, and the nature of complications related to the procedure must all be well documented.

A specific risk/benefit analysis must be carried out and should form part of the submission for any drug delivery system that would require a surgical procedure such as insertion in the subcutaneous tissue.

4.2 Serious and Rare Adverse Events

Clinical trials generally include a sample size that cannot provide definitive information on rare adverse events, e.g. cancer, cardiovascular complications, venous thromboembolism (VTE). Comparative pharmacodynamic data, which should be presented, may indicate possible differences between products but there are no generally well-recognized surrogate end-points for the risk of cancer, cardiovascular events or VTE. However, a careful documentation of serious events should be provided and related to the existence of established predisposing risk factors among the women enrolled in the studies. Post-marketing surveillance of these adverse events must be conducted by the sponsor.

4.3 Other Adverse Events

Information on other adverse events frequently occurring with the use of steroidal contraceptives, e.g. bleeding irregularities, breast tenderness, neurological problems, weight changes, GI effects, etc., should largely come from studies including an active comparator. The comparator should have a similar mechanism(s) of action and schedule of use and be chosen from products marketed in Canada.

Comparative safety data provide important information for the user and the prescriber in choosing preferred methods. Known differences in the spectrum of adverse reactions may also be useful if the first choice is not tolerated.

Important issues such as uterine bleeding abnormalities should be carefully investigated, based on recognized definitions of cycle control analysis (Archer *et al,* 1997; Belsey *et al,* 1986) and using a well-designed diary.

4.4 Follow-up of Pregnancies

All pregnancies occurring during a trial must be followed for final outcome (mother and infant). Data should be collected on teratogenic effects, congenital anomalies and rate of spontaneous abortions and ectopic pregnancies. This information should be analysed in the light of the results obtained from preclinical studies in animals.

REFERENCES

Archer DF, *et al*. A new low-dose monophasic combination oral contraceptive (Alesse®) with levonorgestrel 100 µg and ethinyl estradiol 20 µg. North American Levonorgestrel Study Group (NALSG). *Contraception* 1997; 55 (3): 139-144

Belsey EM, *et al*. The analysis of vaginal bleeding patterns induced by fertility regulating methods. World Health Organization Special Programme of Research, Development and Research Training in Human Reproduction. *Contraception* 1986; 34(3): 253-260

APPENDIX - CONSULTATION

Guidelines for Clinical Development of Steroidal Contraceptives Used by Women

Comments concerning the draft guidelines were solicited from the stakeholders.
Responses were received from two health professional associations, one pharmaceutical manufacturers association, four pharmaceutical manufacturers, and nine health professionals.

Three major issues were raised by most stakeholders who responded to the invitation for commenting on the proposed guidelines. A meeting took place on November 1, 2001 between Health Canada representatives and a panel of experts from the Society of Obstetricians and Gynecologists of Canada to discuss these concerns.

The following summarizes the issues and Health Canada's responses:

1. The proposed duration of the clinical studies

The initial draft guidance document recommended that pivotal trials should last for at least two years in the case of short-acting oral contraceptives.

2. The proposed number of participants in the clinical studies

The initial draft guidance document mentioned that in the case of short-acting oral contraceptives, it is expected that around 800 to 900 participants receiving the study drug will complete 20,000 cycles of exposure.

Most respondants felt that the proposed duration of the clinical studies is excessive and the number of participants is too large, particularly for products which contain active ingredients similar to already marketed contraceptives. It was, however, suggested by some respondants that the Canadian guidelines be harmonized with the corresponding document from The European Agency for the Evaluation of Medicinal Products (EMEA).
Response:

It should be noted that the initial draft guidance document cited specific length of studies and numbers of participants based on experience with the development of new oral contraceptives in North America.

The onus is, of course, on the sponsor of a new drug to provide adequate scientific information and justification to support the safety and efficacy of a proposed product.

A longer period of evaluation for a new short-acting contraceptive is recommended for several reasons such as:

- to demonstrate clearly the contraceptive efficacy of the new product.

- to document good compliance and the sustained use of the study product because compliance and steady use are key factors for demonstrating the efficacy of any contraceptive method.

- to obtain a detailed and reliable profile of possible adverse events associated with the use of the study product. Considering that oral contraceptives may be used for several decades during the reproductive period, collection of this information over a period of two years may be justified.

Regarding the number of participants in the clinical studies, consideration should be given to important demographic factors (age, weight, race, smoking habits, associated health conditions, etc.) which can influence both the efficacy and safety of steroidal contraceptives. It is essential that the sampling of participants in pivotal trials be large enough to assure appropriate representation from critical subpopulations.

- In response to the comments received on both issues, corresponding section of the draft guidance document has been revised to omit the specification for expected number of participants and to elucidate the duration of the studies. The revised section now reads:

  "In the case of short-acting oral contraceptives, pivotal trials should be of adequate length and include adequate number of participants. While efficacy of certain drug products may be established after 12 months of exposure, it is expected that a subgroup of participants in the pivotal trials will be followed for up to 2 years to adequately document both compliance and safety of the study product.

  For long-acting products (e.g., implants, medicated IUDs, etc.), whose efficacy is expected to last for at least 5 years, pivotal trials should be of similar length (at least 5 years). It should be emphasized that pivotal trials must always last for the recommended duration of efficacy. The number of participants should be sufficient to define a precise Pearl Index as mentioned above."

- The following section has been added to clarify the situations which may warrant further reduction in requirements:

"3.4 Reduced requirements in special circumstances

In case of MINOR modifications of marketed products in Canada, requirements for the clinical studies may be reduced and consultation with the appropriate authorities of Health Canada is recommended.

As an example, lesser number of cycles may be required provided that:

- ***pharmacodynamic studies depict at least an equivalent effect on ovarian function comparable with the existing product.***

- ***the reference product has a well documented efficacy and safety profile."***

3. The requirement for endometrial biopsies:

The initial draft guidance document recommended that endometrial biopsies be obtained at baseline, then annually and as deemed necessary.

Most respondants felt that the requirement for endometrial biopsies is unjustified, particularly for nulliparous women. Some indicated that "Ethics Boards" may not approve protocols involving "a painful procedure such as an endometrial biopsy."

Response:

Health Canada agrees that nulliparous women may be excluded from undergoing such testing.

It should be appreciated that the endometrium is one of the main target tissues of steroidal contraceptives that are directly and continuously influenced by the intake of these drugs. One of the most common adverse events associated with the use of steroidal contraceptives is irregular uterine bleeding. This problem is often followed by the discontinuation of such contraceptive method with the potential risk of unplanned pregnancy while waiting for adequate medical evaluation. It is therefore important to investigate carefully the effects of steroidal contraceptives on the endometrium.

The use of endometrial biopsies is the least invasive technique that can provide the histopathological effects of steroidal contraceptives at the level of the endometrium. Such histological examination can often explain the mechanism of irregular uterine bleeding.

The biopsies will help to differentiate between underlying endometrial pathology and undesired side effect of steroidal contraceptives on this tissue. As steroidal contraceptives may now be prescribed up to the age of menopause, a significant portion of participants in these clinical studies may be at risk of developing gynecological pathologies.

The purpose of baseline endometrial biopsy is mostly to exclude enrollment of women with significant endometrial pathology that could be aggravated by the use of steroidal contraceptives. This procedure could be avoided in women without any gynecological symptoms. On the other hand, it would be neither safe nor ethically acceptable to allow the intake of such study drugs for many months by participants without any histological assessment of the endometrium before leaving the clinical trial. Therefore, for safety reasons, it would be desirable to obtain endometrial samples at the end of the clinical trial and at any time during the study if abnormal uterine bleeding occurs.

Use of ultrasonagraphy for measurement of endometrial thickness may be helpful to screen endometrial changes. Unfortunately, to-date no adequate data exist to correlate results of ultrasonography with endometrial biopsies. In the absence of such data, it is unreasonable to assume that ultrasonography would establish, with as much accuracy as histological examination, the nature of endometrial changes.

In essence, the usefulness of endometrial biopsies cannot be understimated in evaluating the safety risks of short-acting steroidal contraceptives.

- As a response to stakeholders' concerns about endometrial biopsies, the guidance document has been modified to remove the above requirement and the following statement has been added:

  "For an adequate safety assessment, whenever possible, endometrial biopsies should be obtained when the participants leave or complete the study. This endometrial biopsy is particularly important when an active component of the study drug constitutes a new chemical entity. Other circumstances which should justify the use of endometrial biopsies are the following: women over the age of 35 years, irregular uterine breakthrough bleeding,, excessive uterine withdrawal bleeding, and detected endometrial anomaly at ultrasound evaluation. Ultrasound evaluation of the endometrium can not replace endometrial biopsy for adequate endometrium evaluation but may be complementary."